THE BURDEN OF ADHESIONS

Richard ten Broek

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ISBN/ EAN 978-94-6203-633-8

Cover and lay-out by R.P.G. ten Broek
Printing: CPI- Koninklijke Wöhrmann
CD-ROM: deCDperserij.nl

Unrestricted financial support was received for publication of this thesis, please visit the sponsor page on the CD-ROM

The Burden of Adhesions

Proefschrift

ter verkrijging van de graad van doctor

aan de Radboud Universiteit Nijmegen

op gezag van de rector magnificus prof. dr. Th.L.M. Engelen,

volgens het besluit van het college van decanen

in het openbaar te verdedigen op vrijdag 31 oktober 2014

om 10.30 uur precies

door

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geboren op 16 februari 1986

te Tilburg

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In blessed memory of my father, Gerardus ten Broek

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Chapter 1: General Introduction and Outline of Thesis

Abstract
The peritoneum mesothelium is a nearly invisible single cell thick layer covering the abdominal wall and the organs within the abdomen, forming the largest serous membrane in the human body. Abdominal surgery per definition traumatizes this peritoneum. Such operations are frequently performed by a multitude of specialists, such as general, vascular, urological and gynaecological surgeons. In the SCAR study, 54 380 patients included during one year had abdominal surgery in Scotland which was more than one per cent of the entire population. In the Netherlands more than 24 000 operations of the lower gastro- intestinal tract are performed annually, procedures with high risk of adhesion formation.
Adhesions form in 60% to 90% of patients after abdominal surgery. Postoperative adhesions cause a life-long risk of different complications including small bowel obstruction, difficulties at re-operations, chronic abdominal pain, and secondary female infertility. These complications can be found after all types of abdominal surgery, performed by surgeons, gynaecologists or urologists.
Till date most reports on the clinical and socioeconomic impact of adhesion related complications has focused solely on adhesive small bowel obstruction. Adhesiolysis at repeat surgery has received much less attention in literature. Underestimation of the related morbidity , may account for the paucity of reports on the consequences of adhesiolysis. Adhesion prevention is also seldom applied. Since the 90's several adhesion barriers have been developed and marketed. Still, many questions exist among surgeons and gynaecologists on the use of adhesion barriers. Only a minority of surgeons have applied an adhesion barrier. In the current thesis the awareness of clinicians of adhesion related complications is investigated, the impact of adhesions at repeat surgery is extensively studied and the current knowledge of adhesion prevention is systematically reviewed.

Adhesions in historical perspective

The oldest reference of adhesions as a response to tissue injury in literature dates back to the year 440; adhesions of the lung were described in the Talmud, a central textbook of Jewish law, as a sign of pleural perforation rendering an animal carcass unsuitable for human consumption (Fig 1). From then it took centuries before adhesions caught the attention of clinicians. It was until the late 19th century when laparotomy became a fairly safe procedure by advances in anaesthesia and antisepsis, that peritoneal adhesions were increasingly recognized as a cause of late complications in abdominal surgery.

In 1872 Bryant described one of the first cases of bowel obstruction caused by peritoneal adhesions, which in this case followed upon ovarian surgery.(1) An unsuccessful attempt to surgically relieve a bowel obstruction four years after ovarian surgery was described in 1883.(2) Shortly thereafter surgeons started attempts to prevent adhesions using different methods, from distending the abdomen with fluid, to omental grafts, and a solution of sodium salicylate to dissolve fibrin.(3-5)

All these efforts did not seem to reduce the problem of intra-abdominal adhesion formation. With these failures came disappointment and pessimism about adhesion prevention.(6) Subsequently, clinical interest and research on peritoneal adhesion formation and prevention had declined for many decades.

A revival of interest in adhesions came about when Ellis et al. in 1999 published land mark data on the consequences of adhesions from a large epidemiological study. In the first ten years after surgery as many as 34.7% of patients were readmitted to hospital for complications that were probably adhesion related.(7) Biomedical industry developed several barriers to prevent adhesion formation, some of which seemed effective in reducing adhesion formation and were registered for clinical use.(8-12) Several trials assessing efficacy of such barriers were conducted, the largest of which included 1791 patients undergoing colorectal surgery.(9)

In the Netherlands several surgical groups started to perform research on etiology, epidemiology and prevention of adhesions. The group from Nijmegen was one of the first to study the problem of adhesiolysis in repeat surgery;(13;14) The group from Rotterdam studied laparoscopic adhesiolysis for chronic pain;(15) Adhesions to meshes used for incisional hernia repair is focus of research in Maastricht;(16;17) The group from Leiden studied pathophysiology of adhesions and the role of tissue plasminogen activator in gynaecological surgery.(18;19)

Despite these efforts and the development of new biomaterials that reduce adhesion formation, use of adhesion barriers remains low.(20;21) Questions remain whether reducing adhesion formation will alleviate the burden of adhesion related complications, whether or not adhesion barriers are cost- effective, and if adhesion barriers are beneficial in addition to minimal surgical trauma such as in laparoscopy.(11;12;20;21)

In 2008 the Dutch Adhesion Group was founded to increase awareness of adhesion related problems and prevention, and to stimulate research on adhesions in the Netherlands. In this group surgeons and gynaecologists act together to combat adhesions. Research ideas generated within this group are elaborated in the epidemiological studies in this thesis.

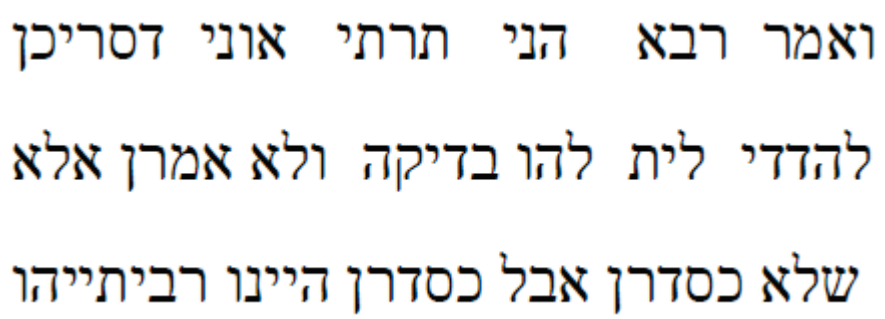

Figure 1 Passage from the Talmud on pleural adhesions.

Babylonian Talmud, Tractate Chullin, page 46b. Translation of the passage ` Raba further said: If two lobes of the lungs adhere to each other [by fibrous tissue], no examination thereof can avail [to render the animal permitted]. This is so, however, only if the lobes were not adjacent, but if they were adjacent [it is permitted, for] this is their natural position.´

Pathology of Peritoneal Adhesion Formation

The peritoneum mesothelium is a nearly invisible single cell thick layer covering the abdominal wall and the organs within the abdomen, forming the largest serous membrane in the human body. Abdominal surgery per definition traumatizes this peritoneum. Such operations are frequently performed by a multitude of specialists, such as general, vascular, urological and gynaecological surgeons. Exact enumeration of peritoneal operations is difficult because of different coding systems used. For example, in the year 1986, 54 380 patients had abdominal surgery in Scotland which is more than one per cent of the entire population.(7) In the Netherlands more than 24 000 operations of the lower gastro- intestinal tract are performed annually [PRISMANT], procedures with high risk of adhesion formation. In any abdominal operation, whether performed via laparotomy or laparoscopy, damage to the peritoneum is inevitable (Table 1). Usually, the peritoneum quickly restores from surgical injury. Already in 1919 Hertzler found that, unlike the relative slow healing from the borders in tissues such as skin "the entire surface of the peritoneum becomes ‘epithialized’ simultaneously and not gradually from the borders".(22) Raftery showed that this healing process is complete in about one week in rats.(23)

Table 1 List of factors contributing to peritoneal injury during abdominal surgery

Factor:
Disruption of peritoneum at entry (incision or trocar)
Local ischemia
Foreign bodies (stitches, mesh, powder)
Contamination (faecal, blood)
Electrocoagulation devices
Tissue handling
Evaporation (exposure to dry air, pneumoperitoneum)
Light

Several hypothesis have been formed on the origin of the colonizing cells that cover the peritoneal defect:(24)

1. Growth from peripheral cells
2. Transformation of underlying mesenchymal (stem) cells
3. Transplantation of mesothelial cells from adjacent structures or free floating mesenchymal cells
4. Transformation of cells from the peripheral fluid.

After peritoneal damage fibrinous bands, connecting opposing damaged areas, are formed as part of the healing process. Physiologically, such band are resolved by the fibrinolytic system resulting in 'ad integrum' repair. This fibrinolytic system is activated by the action of tissue plasminogen activator (tPA). tPA turns plasminogen into the active plasmin that splits the fibrinous bands.(25) During inflammation the fibrionolytic system is inhibited by release of plasminogen activator inhibitor (PAI) and if the net result of fibrinolysisis activators and inhibitors is decreased, fibrinous bands will turn into more permanent fibrous bands named adhesions.(26) Morphology of adhesions can widely differ from loose rag-like bands to dense matted adhesions with ingrowths of blood vessels en nerve tissue.
The amount of PAI secreted seems to correlate with the degree of tissue injury and inflammation. The equilibrium between fibrinolytic activity and its inhibtion is influenced by many factors, which mechanism is not fully understood. However, it is clear that the release of many inflammatory cytokines, growth factors and enzymes such as matrix metalloproteases, TGF-beta1, TGF-beta3, tachykinins, and INF-gamma contribute to adhesion formation.(27-29)

Clinical implications of adhesion formation

Adhesions form in 60% to 90% of patients after abdominal surgery.(30;31) Adhesions are the most common cause for long term morbidity following abdominal surgery. Postoperative adhesions cause a life-long risk of different complications including small bowel obstruction, difficulties at re-operations, chronic abdominal pain, and secondary female infertility. These complications can be found after all types of abdominal surgery, performed by surgeons, gynaecologists or urologists.(7;32;33)
Three SCAR studies report results on the burden of adhesions.(7;32;33) The first SCAR study described a cohort of 29,790 patients who underwent peritoneal surgery in 1986 and had no history of prior surgery in the last 5 years. After 10 years follow-up, overall, 34.7% of patients were readmitted to a hospital with a mean of 2.1 episodes of readmission per patient. Among these readmission, a rate of 4.1 readmissions directly related to adhesions per 100 initial procedures was found at ten years follow-up and a rate of 27.7 readmissions possibly related to adhesions. Moreover, forty reinterventions per 100 patients were carried out that might have been complicated by adhesions.
Such reinterventions can be time consuming, difficult and potentially dangerous as a result of adhesion formation. In a study by van der Krabben et al. almost one in five patients undergoing abdominal repeat surgery sustained inadvertent bowel injury.(13) Most readmissions directly related to adhesion formation are for adhesive small bowel injury. Hospital mortality from adhesive small bowel obstruction is estimated at 4.0 to 7.5%.(34;35)

A conservative estimate of the costs associated with an episode of readmission for small bowel obstruction is between EUR€1500- 2600 when conservatively treated and between EUR€3300- 7500 when operatively treated.(36-38) In the United States this results in US$2 billion of annual health-care costs associated with adhesive small bowel obstruction.(39) Extrapolated to the Dutch situation, this corresponds with EUR€10 million annually. Chronic pelvic pain affect nearly 15% of women between 18 and 50 years of age, resulting in almost US$ 900 million of annual costs from gynaecological consultations in the United States.(40) However, not all of these cases of chronic pain is caused by adhesions.
Ellis reported a series of articles on medicolegal claims related to abdominal adhesions in a small series of articles (Table 4).(41-43) A total of 173 claims was analyzed. Visceral injury following adhesiolysis was the most frequent reason to claim; 69 (39.3%) claims. In five claims related to visceral injury the patient died, in four of these the claim was granted. Other frequent reasons for claims were failed diagnosis, pain and infertility. At least 29 of 67 claims that are registered at the National Health Service Litigation Authority between 1995 and 2007 have been granted. The incidence of adhesion related complications is well above the threshold at which providing no information during informed consent can be deemed negligence. The data regarding adhesion related claims illustrates the legislative consequences of such negligence.

Repeat surgery and adhesions

Till date most reports on the clinical and socioeconomic impact of adhesion related complications has focused on adhesive small bowel obstruction. Adhesiolysis at repeat surgery has received much less attention in literature. Underestimation of the related morbidity and the passiveness of many physicians, who consider adhesiolysis an annoying but unavoidable part of redo surgery, may account for the paucity of reports on the consequences of adhesiolysis.
However, adhesiolysis might actually cause a higher burden of morbidity and costs than adhesive small bowel obstruction. Although morbidity from adhesive small bowel obstruction is high, the incidences are relatively low. Today, as many as 40- 66% of elective procedures in general surgery are reoperations.(9;44;45) Prolonged operation time, bleeding, trocar injury, conversion from laparoscopy to laparotomy and damage to peritoneal organs such as bowel, liver, spleen, bladder, or ureter, are all well-known intra-operative complications of adhesiolysis.(46)
All these intra- operative complications contribute to higher morbidity and prolonged convalescence in patients undergoing repeated abdominal surgery compared patients with no history of abdominal surgery undergoing to the same procedure. In open abdominal surgery, 39% major complications and 8% mortality were found in a mixed group of 270 patients who underwent abdominal re-operation through a pre-existent scar.(13)
This number of repeat abdominal operations is only expected to rise because of a longer life expectancy and newer technologies. A better understanding of the morbidity and costs associated with repeat surgery and adhesiolysis is necessary to properly inform patients and evaluate cost effectiveness of adhesion reducing strategies.

Adhesion prevention

Albeit limited, the available data on the burden of adhesion related complications prompt action to reduce postoperative adhesion formation. The actual burden of adhesions is probably even much higher than the estimates from literature. Almost all epidemiological and socioeconomical studies to the impact of adhesions have used rather conservative methods and available cost models have also not taking into account repeat surgery problems, sick leaves, therapies for secondary fertility etc.
Adhesion reducing agents can grossly be divided into two groups, systemic acting pharmacological agents and local acting adhesion barriers. The use of systemic acting agents, mainly steroids, has been abandoned because of disappointing results in trials and the risk of serious adverse events.(12)
The concept of local acting adhesion barriers is that they do not interfere with normal tissue healing, but rather act as a spacer separating opposing sites of regenerating peritoneal and serosal layers. Such barriers are made in several biochemical formulas: solid membrane, viscous gel or liquid. The latter two are more practically applied in laparoscopy.
Safety has been established in large clinical studies for several of these barriers.(9;47;48) Meta-analysis from randomized trials also have demonstrated that some of these barriers have the potential to reduce adhesion formation.(11;12)
Still, many questions exist among surgeons and gynaecologists on the use of adhesion barriers. Only a minority of surgeons have applied an adhesion barrier.(20;21) Most barriers have only been studied in gynaecological surgery. Hyaluronate carboxy methylcellulose is the only barrier studies in a large trial of patients undergoing colorectal surgery.(9) Moreover, surgeons question whether the reduction in adhesion formation will also truly alleviate the burden of adhesion related disease, if reduced adhesion formation will not interfere with anastomotic healing and if adhesions barriers are cost- effective.

In summary, postoperative adhesions remains an almost neglected problem by both clinicians, policy maker and patients, and anti-adhesive strategies seems still in their infancy of acceptance and routine use.
In the current thesis the awareness of clinicians of adhesion related complications is investigated, the impact of adhesions at repeat surgery is extensively studied and the current knowledge of adhesion prevention is systematically reviewed.

Part I: Awareness of adhesion related complications
To obtain successful implementation of evidence based adhesion prevention strategies both knowledge and attitude of physicians regarding clinical impact of adhesions need to be addressed. Current epidemiological knowledge mainly comes from studies defining readmissions as a proxy for the impact of adhesions, which lacks detailed information regarding the morbidity and impact of several complications of adhesions.(7;32;33) Data on the separate clinical entities related to adhesion formation (small bowel obstruction, infertility, difficulties at re-operations and chronic abdominal pain), are difficult to overview, and different outcome measures are used in literature. A comprehensive review of these separate clinical entities provides a more readily interpretable estimate of the disease burden related to adhesions and will increase awareness. In **chapter 2** we systematically reviewed and analyzed the incidence of the four most important complications of postoperative adhesion formation

(small bowel obstruction, difficulties at repeated abdominal surgery, female infertility, and chronic pain) following all types of abdominal surgery.

Patients with adhesion related complications are often treated years later by other specialists than the surgeon who performed the first operation. The first surgeon therefore remains unaware of the complication. This may significantly impact the knowledge of surgeons of (the prevalence of) adhesion related complications, as well as awareness and attitude of surgeons towards the clinical impact of adhesions and the value of adhesion prevention. We investigated in **chapter 3** the knowledge and awareness of surgeons regarding adhesion related complications and the prevention of adhesions by a nationwide survey.

In **chapter 4** we investigated the accuracy by which adhesions were identified during reoperations and the complications from adhesiolysis were reported, by comparing the text in the operative reports with the real time operative findings in a prospective observational study. The accuracy at which adhesions and related complications are reported may reflect the awareness of the surgeon about the operative significance of adhesions and adhesiolysis.

Part II: Difficulties of adhesions during reoperations

In the second part of this thesis the focus is on morbidity resulting from adhesiolysis during repeat operations. There is marked paucity on data regarding this complication of adhesion formation including factors that predict adhesiolysis related morbidity. **Chapter 5 and 6** describe the morbidity and socio-economic costs resulting from adhesiolysis and subsequent organ injury in a large prospective cohort of elective abdominal operations. In **chapter 7** we report the development of a prognostic model predicting the risk for bowel injury in elective abdominal surgery.

Part III: Adhesion prevention

In the third part strategies to prevent adhesion formation are reviewed. The first step in preventing post-operative adhesions is considered a so-called ‘good surgical technique’ minimizing injury to serosal surfaces and the parietal peritoneum. The significance of minimizing peritoneal injury has been emphasized in numerous reports, however, without substantiating what constitutes a good surgical technique or measure. Aspects of surgical technique often mentioned in literature to be associated with (a reduction of) adhesion formation are laparoscopy, closure of the parietal peritoneum, foreign bodies (e.g. glove powder, sutures and meshes), electrocautery, infection(prevention) and peritoneal lavage. Some studies show conflicting results. In **chapter 8** the available evidence on the impact of surgical technique on adhesion formation is evaluated in a systematic review.
In **chapter 9** local and remote experimental peritoneal injury is compared by using microdialysis, between two routinely used haemostatic and dissection devices, the electrocautery knife and the harmonic scalpel.
Many specialists operating in the abdominal cavity are unfamiliar with the indication and use of adhesion prevention agents, despite numerous clinical trials and three Cochrane reviews. The many questions that exist about the indications for adhesion barriers, whether reducing adhesions is also correlated with reduction in adhesion related complications, whether barriers

are cost-effective, and which barrier should be used in which circumstances are possible explanations for the limited routine use of adhesion barriers. In **chapter 10** results of a new systematic review on adhesion prevention agents that are approved for clinical use by the Food and Drug Adminstration are presented using a recently developed error-matrix approach. In **chapter 11** the results are reported of a pilot study on the efficacy of a polyethylene glycol adhesion barrier in gynaecological laparoscopic surgery. The difficulties encountered in such an adhesion prevention study are discussed and give insight in the reason for bias of some studies reviewed in chapter 10.

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PART I: Awareness of adhesion related complications

Chapter 2: Burden of adhesions in abdominal and pelvic surgery: systematic review and meta-analyses

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Published in: BMJ 2013;347:f5588

Abstract

Objective

To estimate the disease burden of the most important complications of postoperative abdominal adhesions: small bowel obstruction, difficulties at reoperation, infertility, and chronic pain.

Design

Systematic review and meta-analyses.

Data sources

Searches of PubMed, Embase, and Central, from January 1990 to December 2012, without restrictions to publication status or language.

Study selection

All types of studies reporting on the incidence of adhesion related complications were considered.

Data extraction and analysis

The primary outcome was the incidence of adhesive small bowel obstruction in patients with a history of abdominal surgery. Secondary outcomes were the incidence of small bowel obstruction by any cause, difference in operative time, enterotomy during adhesiolysis, and pregnancy rate after abdominal surgery. Subgroup and sensitivity analyses were done to study the robustness of the results. A random effects model was used to account for heterogeneity between studies.

Results

We identified 196 eligible papers. Heterogeneity was considerable for almost all meta-analyses. The origin of heterogeneity could not be explained by study design, study quality, publication date, anatomical site of operation, or operative technique. The incidence of small bowel obstruction by any cause after abdominal surgery was 9% (95% confidence interval 7% to 10%; I^2=99%). the incidence of adhesive small bowel obstruction was 2% (2% to 3%; I^2=93%); presence of adhesions was generally confirmed by emergent reoperation. In patients with a known cause of small bowel obstruction, adhesions were the single most common cause (56%, 49% to 64%; I^2=96%). Operative time was prolonged by 15 minutes (95% confidence interval 9.3 to 21.1 minutes; I^2=85%) in patients with previous surgery. Use of adhesiolysis resulted in a 6% (4% to 8%; I^2=89%) incidence of iatrogenic bowel injury. The pregnancy rate after colorectal surgery in patients with inflammatory bowel disease was 50% (37% to 63%; I^2=94%), which was significantly lower than the pregnancy rate in medically treated patients (82%, 70% to 94%; I^2=97%).

Conclusions

This review provides detailed and systematically analysed knowledge of the disease burden of adhesions. Complications of postoperative adhesion formation are frequent, have a large negative effect on patients' health, and increase workload in clinical practice. The quantitative effects should be interpreted with caution owing to large heterogeneity.

Registration

The review protocol was registered through PROSPERO (CRD42012003180).

Introduction

Postoperative adhesion formation is the most common complication of abdominal or pelvic surgery, which is frequently performed by general, vascular, and gynaecological surgeons and urologists. Unlike other postoperative complications, such as wound infection or anastomotic leakage, the consequences of adhesion formation comprise a lifelong risk for various clinical entities.(1-6) Patients with adhesion related complications are often treated by specialists other than the surgeon who did the first operation. The first surgeon therefore remains unaware of the complication, which might explain the gross underestimation of adhesion related complications among surgeons and gynaecologists.(7-9)

Knowledge of complications is vital in surgical decision making, timely recognition of complications, and informing the patient properly before surgery. Adhesions may cause acute abdomen by bowel obstruction and female infertility, and patients may require reoperation.(5; 6;10-14) Lysis of adhesions is associated with a prolonged operative time and an increased risk of intraoperative and postoperative complications.(5;14) Most of the epidemiological knowledge of adhesions has been derived from the extensive work of the Surgical and Clinical Adhesions Research (SCAR) Group.(4;15;16) They, however, defined readmissions as a proxy for the effect of adhesions, which lacks detailed information on the effect of different adhesive complications. Data on adhesion related complications are reported incidentally, and different outcome measures have been used. However, when studied systematically, the studies published so far will provide a large body of evidence on the effect of adhesion formation.

In this systematic review with meta-analyses, we studied the incidence of the four most important complications of postoperative adhesion formation: small bowel obstruction, difficulties at repeated abdominal surgery, female infertility, and chronic pain. A more valid estimate of the disease burden of adhesions will increase the awareness of this complication, which can be used in counselling and clinical practice.

Methods

Search

Two researchers (RPGtB and YI) searched the Cochrane Central Register of Controlled Trials, PubMed, and Embase from January 1990 to December 2012, using the search terms for small bowel obstruction, incidence and morbidity of small bowel obstruction, female infertility, chronic pain, and history of abdominal surgery listed in the box. We additionally searched the reference lists of included studies, excluded studies, and previous reviews. We included studies irrespective of language or publication status. We carried out the review in accordance with a protocol that was registered in PROSPERO (CRD42012003180) after a first version of this paper was written but before the major revisions were done (Appendix A).

Search strategy

Patients
Intestinal obstruction[mesh] OR "bowel obstruction"[tiab] OR SBO[tiab] OR infertility, female[mesh] OR infertility[tiab] OR enterotomy[tiab] OR abdominal pain[mesh] OR pelvic pain[mesh] OR "abdominal pain"[tiab] OR "pelvic pain"[tiab] OR intestinal disease/surgery[mesh] OR abdomen/surgery[mesh] OR peritoneum/surgery[mesh] OR Laparoscopy[mesh] OR laparotomy[mesh] OR laparo*[tiab]

Intervention
Tissue adhesions[mesh] OR adhes*[tiab]) AND (abdo*[tiab] OR abdomen[mesh] OR pelvis[mesh] OR pelvi*[tiab] OR periton*[tiab] OR Peritoneum[mesh] OR Laparoscopy[mesh] OR laparotomy[mesh] OR laparo*[tiab] OR intestine[mesh] OR intestin*[tiab]

Control
—

Outcome
epidemiology[subheading] OR etiology[subheading] OR incidence[mesh] OR incidence[tiab] OR prevalence[mesh] OR prevalence[tiab] OR economics[subheading] OR legislation and jurisprudence[subheading] OR medicoleg*[tiab] OR cost of illness[mesh] OR "operative time"[tiab] OR "operation time"[tiab]

Limits
Subheadings: NOT (animal NOT human)

Publication date: 1 January 1990 or later

[mesh]=medical subheading, controlled vocabulary as used by National Library of Medicine for indexing articles
[tiab]=word in title or abstract
*=truncation; retrieves all possible suffix variations of root word indicated

Study selection

We selected the studies in two rounds: firstly, on title and abstract, independently by two reviewers (RPGtB and YI); secondly, on full text, also independently by the same two reviewers, against pre-specified criteria. We included studies that reported on adhesion related complications after peritoneal surgery. We excluded case series with less than 10 patients and studies that did not include (trans)peritoneal abdominal surgery (for example, preperitoneal or retroperitoneal surgery). If more than one publication was available, we used either the most recent publication or the one with the most relevant information.

Data extraction

Two reviewers (RPGtB and YI) extracted and checked the data. From the relevant articles, we extracted information on study design, characteristics, number of participants, and outcomes reported.

The primary outcome of interest was the incidence of adhesive small bowel obstruction during follow-up after peritoneal surgery, which we defined as any episode of postoperative

small bowel obstruction with the presence of adhesions confirmed during reoperation or by imaging after exclusion of other causes of bowel obstruction. Secondary outcomes of interest related to small bowel obstruction were incidence of postoperative small bowel obstruction by any cause, the cross sectional incidence of adhesions in all patients with postoperative small bowel obstruction, the number of reoperations for adhesive small bowel obstruction, mortality, and length of hospital stay related to adhesive small bowel obstruction.

Secondary outcomes related to complications during reoperation were the incidence of inadvertent enterotomy and the difference in operative time between patients with and without previous surgery. Secondary outcomes related to infertility were the pregnancy rate following surgery, the pregnancy rate compared before and after surgery, use of fertility treatment following surgery, and incidence of adhesions in patients evaluated for infertility after surgery. We excluded surgical studies on operations that directly affected fertility, such as hysterectomy, bilateral ovariectomy, and sterilisation. The secondary outcomes related to chronic pain were the incidence of chronic pain following surgery and the incidence of adhesions in patients evaluated for chronic pain.

Risk of bias assessment

Two reviewers (RPGtB and YI) independently determined the quality score of non-randomised studies and of subanalyses and retrospective analyses of randomised controlled trials according to the revised version of the Newcastle-Ottawa scale for cohort studies (www.ohri.ca/programs/clinical_epidemiology/oxford.htm), with a maximum score of five stars. Five stars is considered high quality, three to four stars is considered intermediate quality, and one to two stars is considered low quality. We assessed publication bias of included studies with funnel plots.

Data synthesis and analysis

We plotted individual study estimates of incidences and proportions. We used the inverse variance method for pooling the incidences and to calculate the corresponding 95% confidence intervals. As recommended in the Cochrane handbook, we used I^2 tests to measure heterogeneity. We defined an I^2 value between 50% and 75% as substantial heterogeneity and an I^2 value of 75% or above as considerable heterogeneity.(17) As we expected heterogeneity between studies, we used a random effects meta-analysis for the primary analyses. Such a random effects meta-analysis model involves an assumption that the effects being estimated in the different studies are not identical but follow some distribution.(17) If applicable, we made additional forest plots and calculated pooled odds ratios to compare incidences between subgroups (for example, laparoscopy versus laparotomy) and the various anatomical locations (general surgery, upper gastrointestinal tract, lower gastrointestinal tract, hepatobiliary and pancreatic surgery, abdominal wall surgery, gynaecological surgery, urological surgery, and paediatric surgery).

We did sensitivity analyses to study best and worst case scenarios for the missing values. In the best case scenario analyses, we assumed that all dropouts did not have an adhesion related outcome and that all female dropouts became pregnant. In the worst case scenario analyses, we assumed that all dropouts had adhesion related outcomes and none became pregnant. We also did sensitivity analyses on the effect of risk of bias, the effect of single

studies, the effect of the study design (prospective versus retrospective cohort), and the time frame (up to 2000 and after 2000) on point estimates.

We used Review Manager (version 5.0) for all analyses. We followed both the Meta-analysis of Observational Studies in Epidemiology (MOOSE) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in reporting the results.

Results

Search results

Figure 1shows the number of studies identified, reviewed, and selected and the reasons for exclusion. We retrieved 4152 unique citations, of which we considered 546 to be potentially eligible. Twenty three (4.2%) papers could not be retrieved, and we excluded 327 because they reported on cohorts already included, no data on relevant endpoints were found, or the data could not be extracted for a cohort of patients with abdominal surgery in their history. We included 196 studies representing 150 797 patients (Appendix B).

Characteristics of included studies

Studies were available for the analysis of small bowel obstruction (n=125), difficulties and complications at reoperation (n=62), infertility (n=11), and pain (n=5). One hundred and sixty seven studies were done in adults and 27 in children; two studies included both children and adults. Forty one studies included patients with any surgical history, 11 included gynaecological surgery, 13 urological surgery, 79 lower gastrointestinal tract surgery, 21 upper gastrointestinal tract surgery, 16 hepatobiliary and pancreatic surgery, and 15 abdominal wall repair. Most of the included studies were judged to be of intermediate quality (n=125); 44 had a low risk of bias, and 27 had a high risk of bias (appendix C).

Adhesive small bowel obstruction

The incidence of small bowel obstruction following surgery was assessed in 92 studies. The incidence of postoperative small bowel obstruction, by any cause, was 9% (95% confidence interval 7% to 10%; I^2=99%) in 61 studies including 107 949 patients. The incidence of adhesive small bowel obstruction was 2.4% (2.1% to 2.8%; I^2=93%) in 87 studies including 110 076 patients. In general, the presence of adhesions could be confirmed only in patients requiring reoperation. Not surprisingly, the incidence of reoperations for adhesive small bowel obstruction was comparable (2.4%, 2.0% to 2.7%; I^2=91%). The cause of bowel obstruction could be established in 42 studies (including 5390 patients); adhesions seemed to be the most common cause of postoperative small bowel obstruction, accounting for 56% (49% to 64%; I^2=96%).

Best and worst case scenarios for the incidence of adhesive small bowel obstruction could be done using 67 studies (51 281 patients, of whom 3725 (7.3%) were lost to follow-up). In the best case scenario, assuming all patients lost to follow-up did not develop adhesive small bowel obstruction, the incidence was 2.5% (2.0% to 2.9%; I^2=92%). In the worst case scenario, assuming all patients lost to follow-up developed adhesive small bowel obstruction, the incidence was 11.7% (10.1% to 13.2%; I^2=99%). The incidence of postoperative small

bowel obstruction by any cause was 9% (7% to 11%; I^2=99%) in the best case scenario and 15% (12% to 18%; I^2=99%) in the worst case scenario.

The incidence of adhesive small bowel obstruction depended on the anatomical location of previous surgery (Fig 2). The incidence was highest in paediatric surgery (4.2%, 2.8% to 5.5%; I^2=86%) and in lower gastrointestinal tract surgery (3.2%, 2.6% to 3.8%; I^2=84%). The incidence was lowest after abdominal wall surgery (0.5%, 0.0% to 0.9%; I^2=0%), upper gastrointestinal tract surgery (1.2%, 0.8% to 1.6%; I^2=80%), and urological surgery (1.5%, 0.1% to 3.0%; I^2=67%). Similar trends were seen for the incidence of postoperative small bowel obstruction by any cause (appendix D).

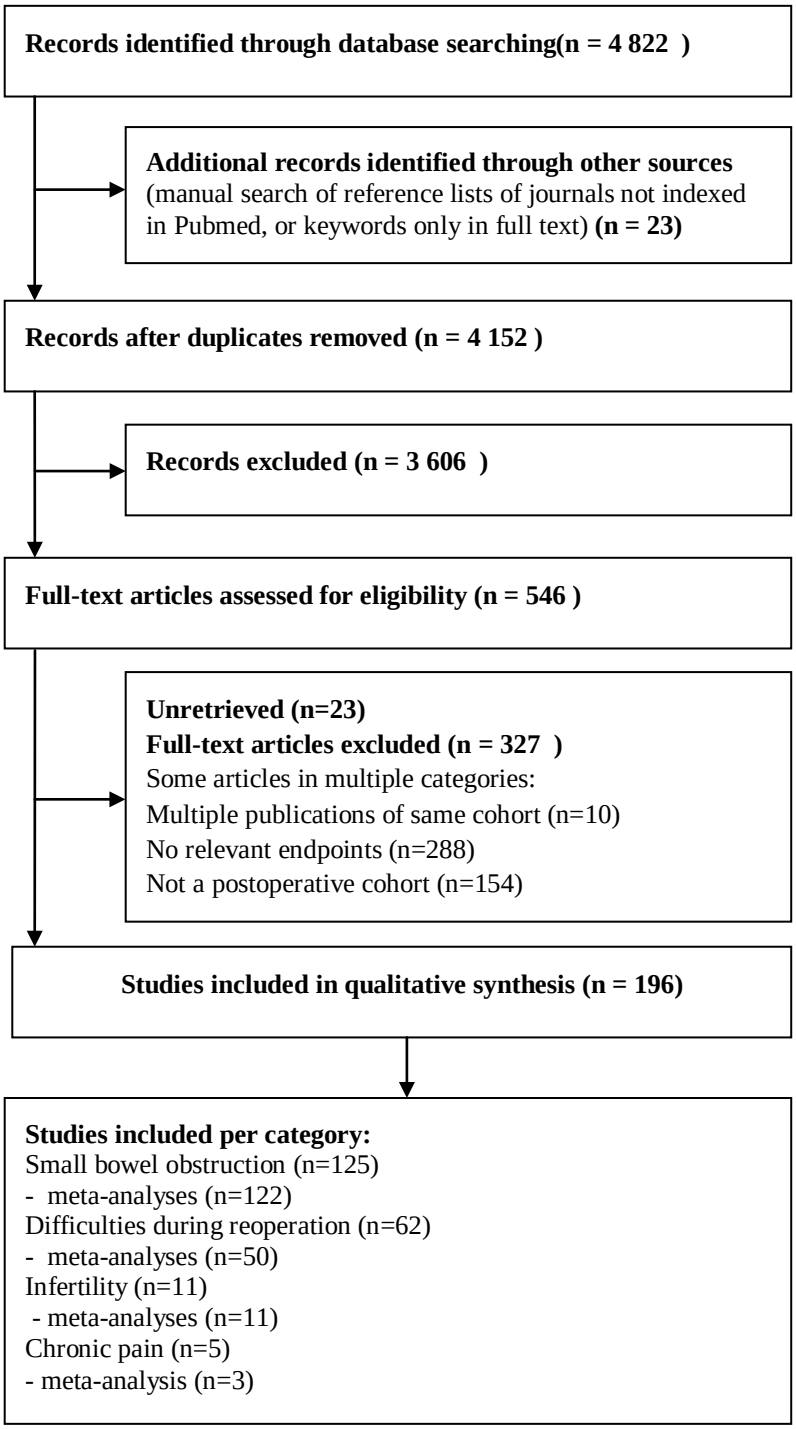

Figure 1 PRISMA flow chart

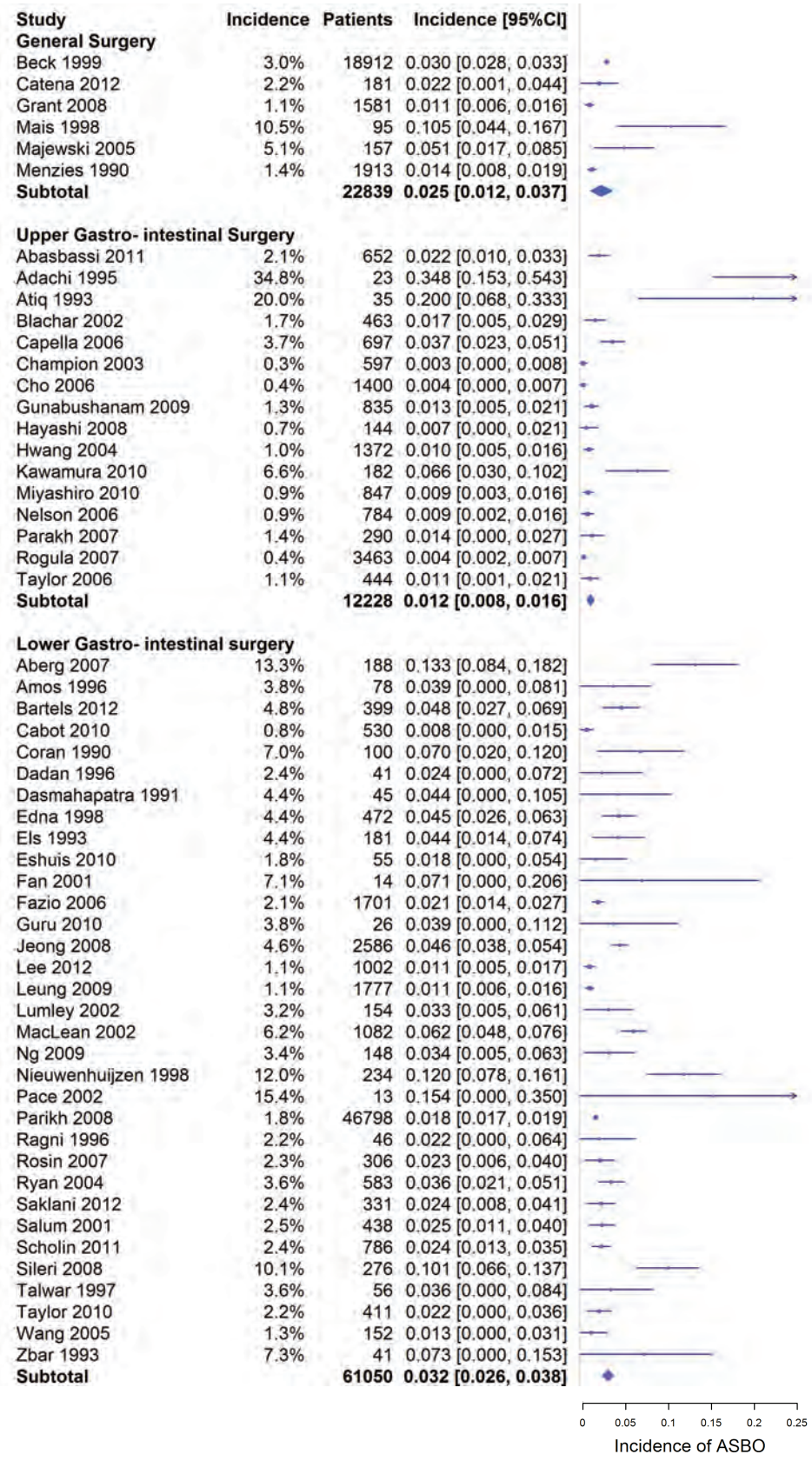

Figure 2 Forest plot of incidence of adhesive small bowel obstruction (ASBO), stratified by anatomical location

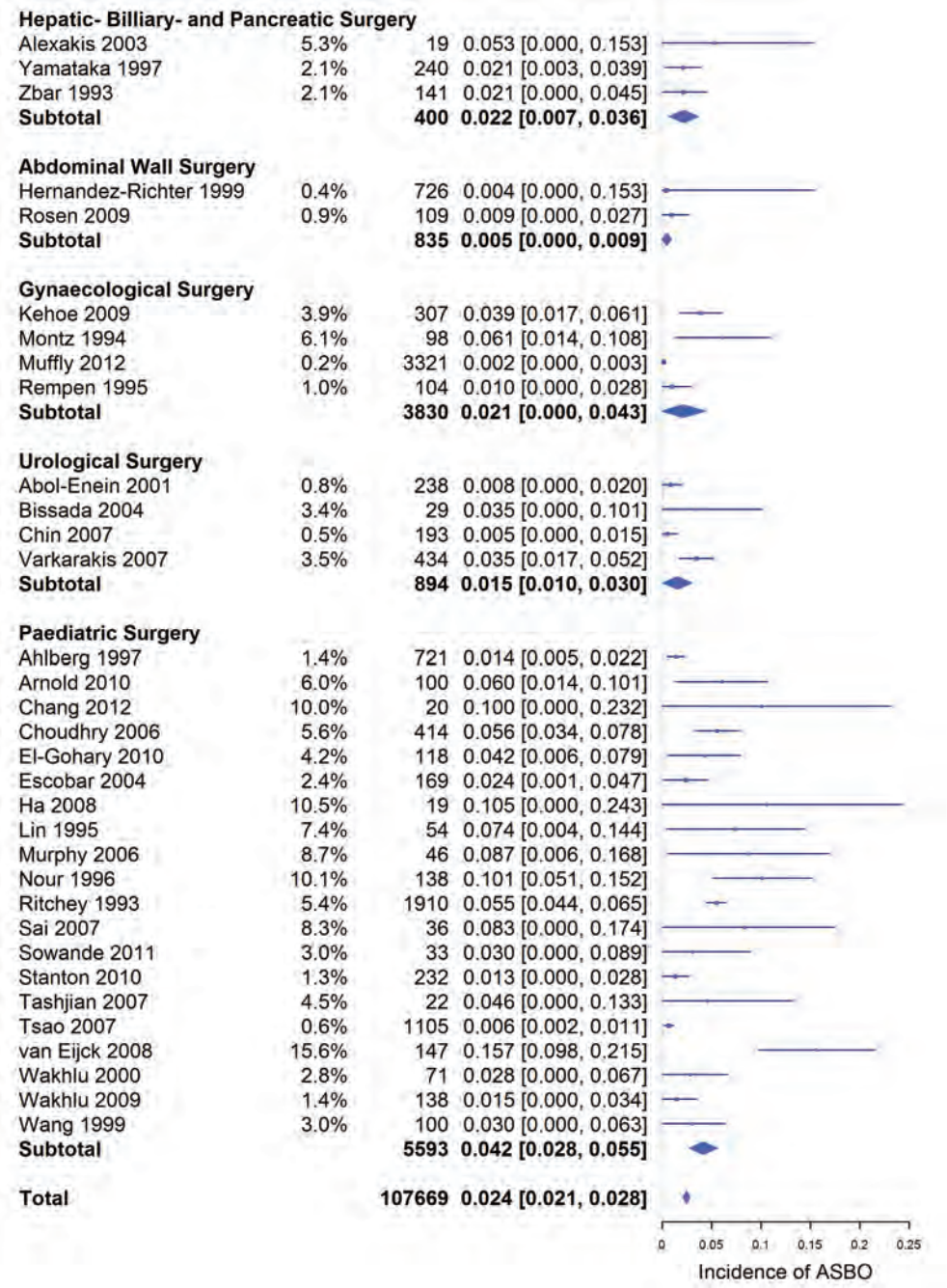

Figure 2 Forest plot of incidence of adhesive small bowel obstruction (ASBO), stratified by anatomical location (continued)

laparoscopic cohorts (1.4%, 1.0% to 1.8%; I^2=86%) than in 54 open surgery cohorts (3.8%, 3.1% to 4.4%; I^2=82%) (Fig 3).The incidence of adhesive small bowel obstruction was also lower after laparoscopic surgery in 10 studies that directly compared laparoscopic and open surgery (odds ratio 0.38, 95% confidence interval 0.16 to 0.91; I^2=37%).

The mean length of hospital stay for small bowel obstruction ranged from 4.4 to 13.4 days in 15 studies (table 1). In five studies included in the meta-analysis, the pooled mean length of stay was7.8 days (95% confidence interval 3.6 to 11.9 days; I^2=0%). Pooled in-hospital mortality from small bowel obstruction, which could be derived in 19 studies, was 2.5% (1.9% to 3.0%; I^2=58%).

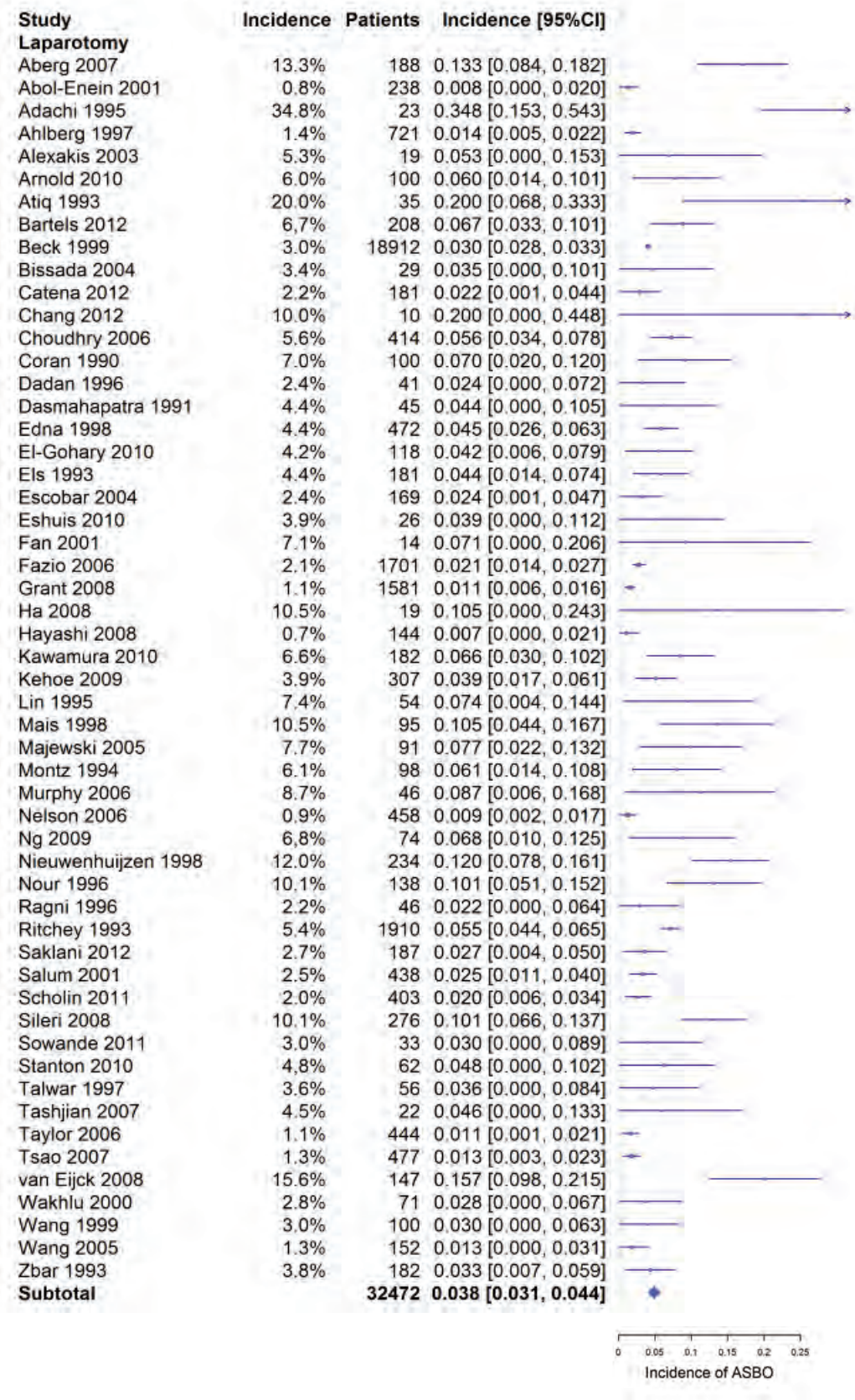

Figure 3 Forest plot of incidence of adhesive small bowel obstruction (ASBO), stratified by laparoscopy and laparotomy

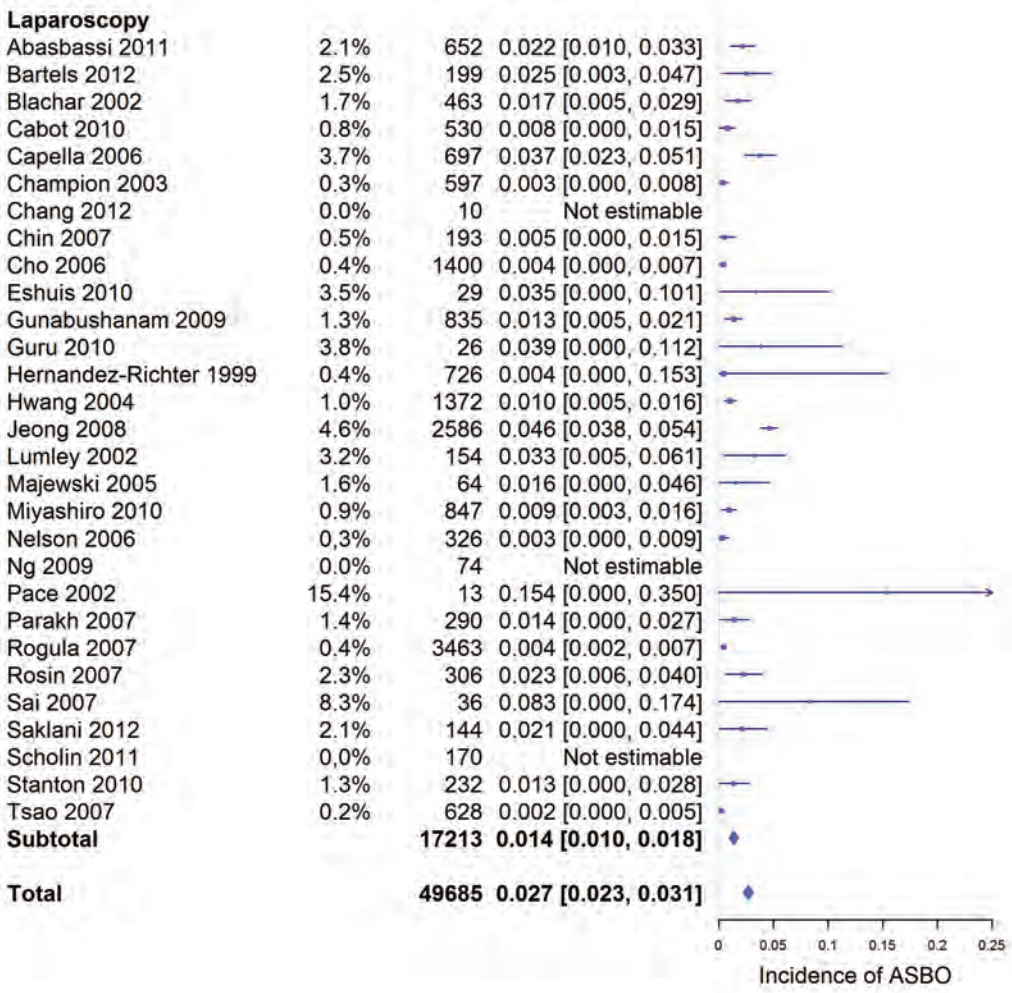

Figure 3 Forest plot of incidence of adhesive small bowel obstruction (ASBO), stratified by laparoscopy and laparotomy (continued)

Table 1 Qualitative analysis of length of hospital stay for treatment of adhesive small bowel obstruction. Values are mean (SD) unless stated otherwise.

Study	Total group		Conservative treatment		Operative treatment	
	No	length of stay [mean ± SD]	No	length of stay	No	length of stay
Alwan 1999	332	8 (0 -156) *	-	-	-	-
Beyrout 2006	258	7 (1 – 63) †	-	-	-	-
Borzellino 2004	65	4.4 (1-22) †	-	-	65	4.4 (1-22) †
Kawamura 2010	10	11.4 ± 7.4	7	11.1 ± 8.9	3	12.0 ± 1.7
Khaikin 2007	72	7-13 ‡	-	-	72	7-13 ‡
Kössi 2004	123	7 ± 0.6	-	-	-	-
Menzies 2001	110	10.5 (1-45) †	69	7 (1-23) †	41	16.3(2 - 45) †
Miller 2002	-	-	23	6 (2 – 33) *	7	12 (9 – 17) *
Miller 2000	-	-	267	4 (NA) *	143	12 (NA) *
Parikh 2008	4555	10.6 ± NA	3429	9.5 ± NA	1126	14 ± NA
Rosin 2000	21	6.9 ± 5.1	-	-	21	6.9 ± 5.1
Shih 2003	293	6.5 ± 3.0	220	6.9 ± 2.9	73	5.9 ± 2.8
Sosa 1993	116	13.4 (2 – NA) †	95	13.7 (2 – NA) †	21	12.3 (6 – 48) †
Suzuki 2003	17	9.9 ± 4.4	-	-	-	-
Wang 2009	46	8.8 (6 – 20)	-	-	-	-

NA= not available

*Median(Range)

† Mean (range), *used only for articles that provided insufficient data to extract mean and SD or median and range.*

‡ Median length of stay 7 in 31 patients receiving laparoscopic surgery, 8 in 10 patients after conversion, and 13 in 31 patients receiving open surgery.

Difficulties at reoperation

The pooled incidence of enterotomy during repeated abdominal surgery was 3.3% (2.5% to 4.0%; I^2=86%) in 39 studies (7654 patients). In 16 studies (2565 procedures) in which the need for adhesiolysis could be confirmed, the incidence of enterotomy was 5.8% (3.7% to 7.9%; I^2=89%). The incidence of enterotomy seemed to depend on the type of surgery. The incidence was highest in lower gastrointestinal tract surgery (8.7%, 3.8% to 13.6%; I^2=84%), followed by gynaecological surgery (4.8%, 0.6% to 9.1%; I^2= 90%). The lowest incidence of enterotomies was found in hepatobiliary and pancreatic surgery (only laparoscopic cholecystectomy) (0.4%, 0.0% to 0.8%; I^2=84%) (Fig 4).

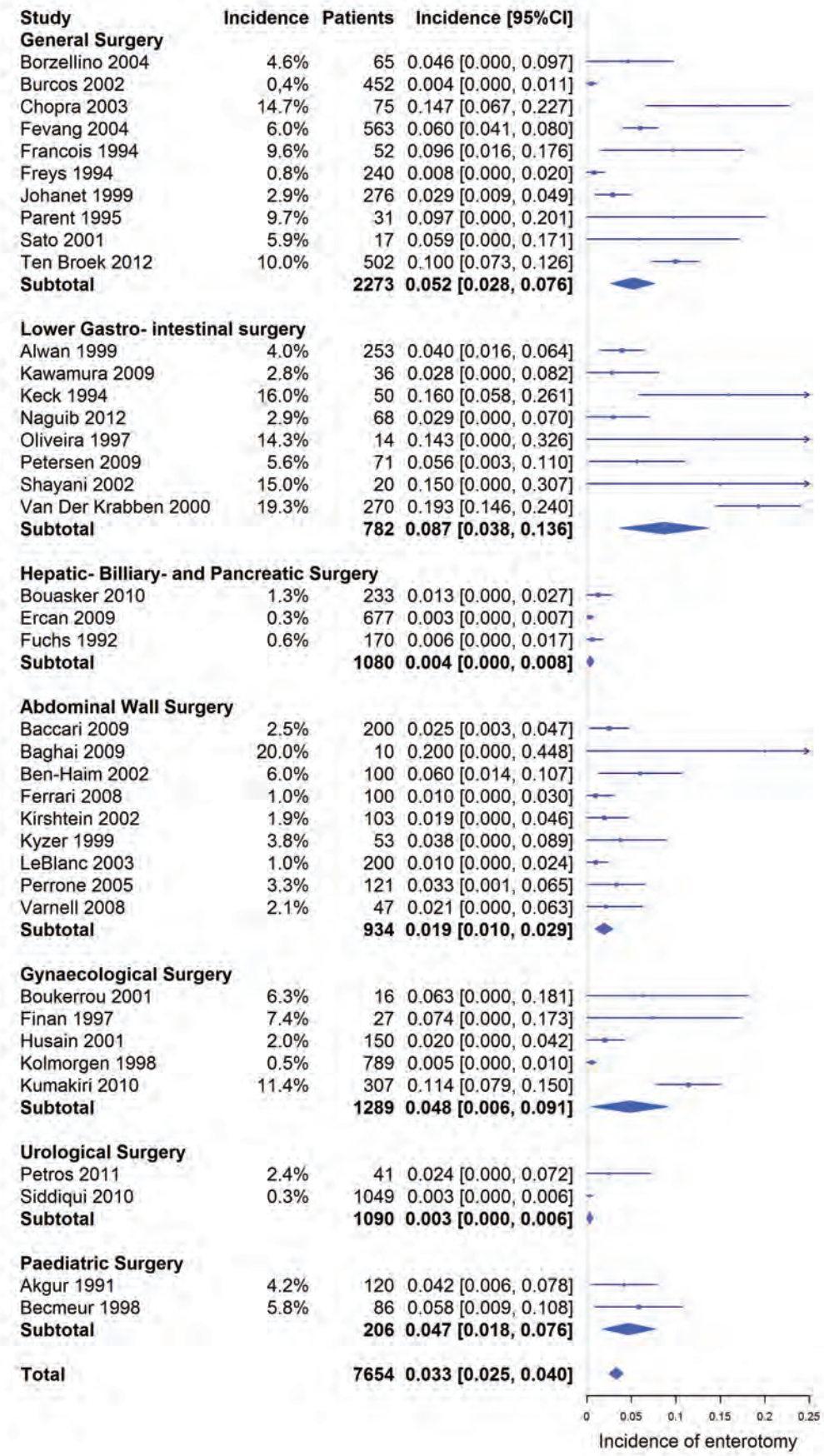

Figure 4 Forest plot of incidence of enterotomy, stratified by anatomical location

The incidence of enterotomy was significantly lower in 30 laparoscopic cohorts (1.8%, 1.2% to 2.4%; I^2=67%) than in eight open cohorts (8.9%, 4.2% to 13.6%; I^2=95%). The same pattern was seen in two studies that compared laparoscopic and open surgery (odds ratio 0.21, 0.05 to 0.90; I^2=0%).

Difference in operative time was reported in 27 studies, of which 13 could be included in a meta-analysis. In 21 studies, operative time was compared between primary and repeat abdominal operation. Operative time was increased in the repeat surgery group in 15 studies and comparable in six studies. The other six studies compared repeated abdominal surgery in which an adhesion barrier had or had not been used during the preceding surgery. In five studies, a reduction of operative time was found after barrier use.

The meta-analysis including 13 studies showed that operative time increased by 15.2 minutes (95% confidence interval 9.3 to 21.1 minutes; I^2=85%) in the repeated surgery group and varied with the anatomical location of the surgery (Fig 5). The increase in operative time did not differ between open and laparoscopic studies.

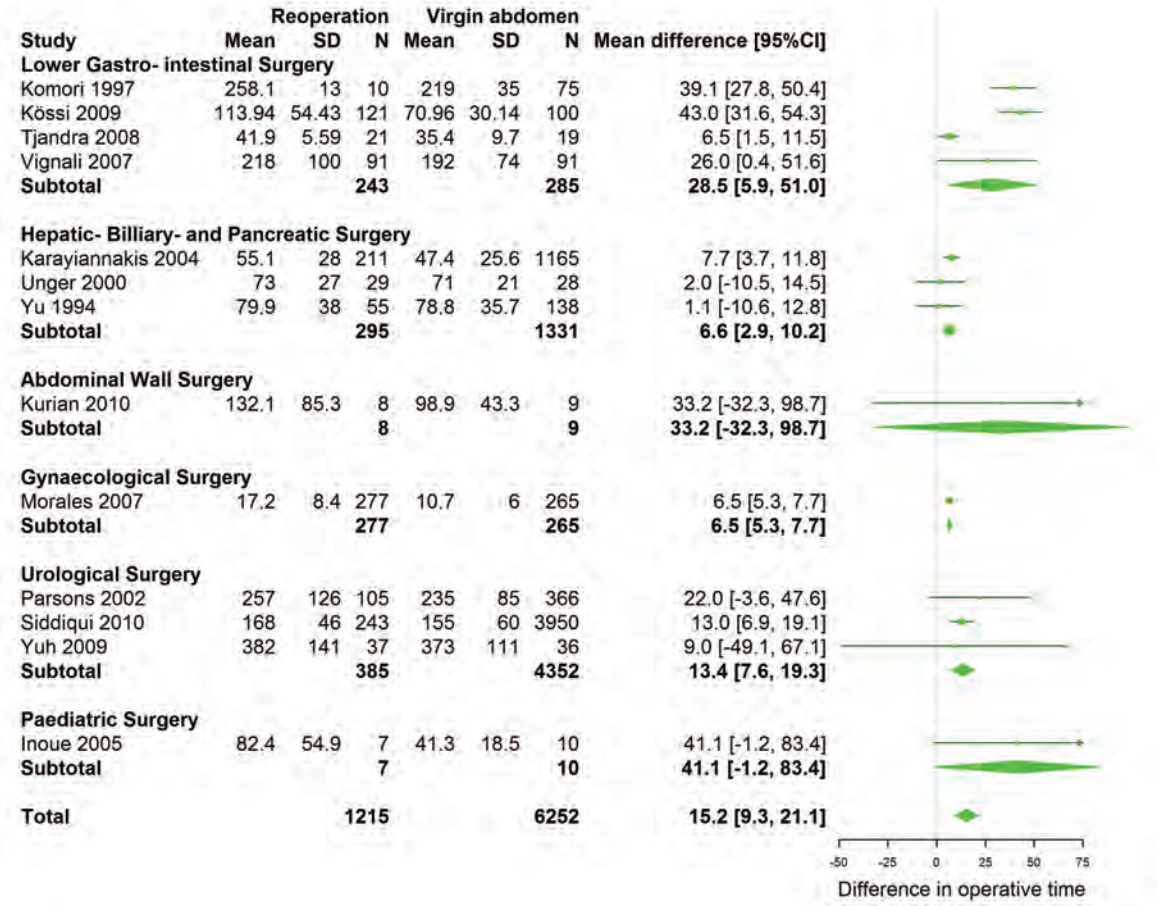

Figure 5 Forest plot of operative time, stratified by anatomical location

Infertility/pregnancy

The pregnancy rate after colorectal surgery for inflammatory bowel disease was 50% (37% to 63%; I^2=94%) in 10 studies including 1004 patients attempting pregnancy, with a range in follow-up from 12 to 158 months. Nine studies compared the fertility rate in patients after the operation with that in patients before the operation or with that in patients treated medically. In all studies, the fertility rate was significantly lower in the operated group than in the non-

operated group, in which the pregnancy rate was 82% (70% to 94%; I^2=97%); the overall odds ratio was 0.15 (0.08 to 0.29; I^2=82%) (Fig 6). The pregnancy rate was 65% (52% to 78%; I^2=97%) in the best case scenario and 38% (23% to 53%; I^2=98%) in the worst case scenario. In three studies, 23% (18% to 29%; I^2=19%) of postoperative patients required fertility treatment.

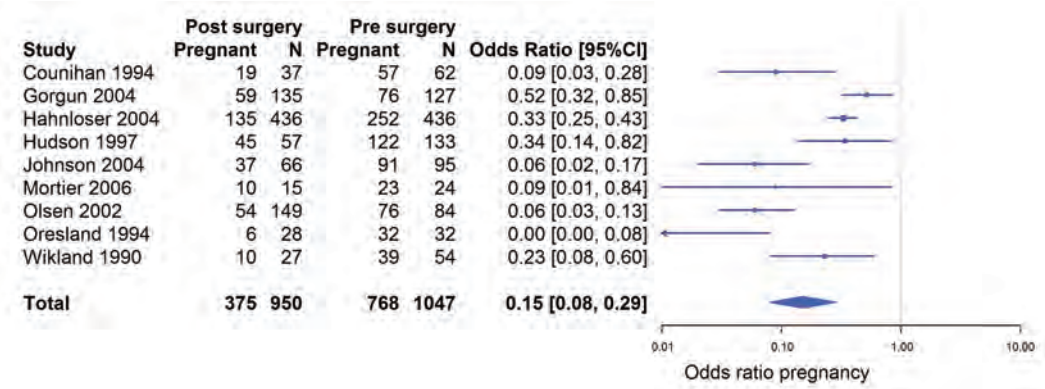

Figure 6 Forest plot of pregnancy rate compared between operated and not operated patients

Chronic abdominal pain

In one study following 198 patients after lower gastrointestinal tract surgery for adhesive small bowel obstruction, 40% (34% to 47%; I^2=not applicable) of patients developed chronic abdominal pain. In four studies following patients with chronic postoperative pain after previous surgery, adhesions were identified as the most likely cause of pain during diagnostic laparoscopy in 57% (47% to 67%; I^2=77%) of patients (Fig 7).

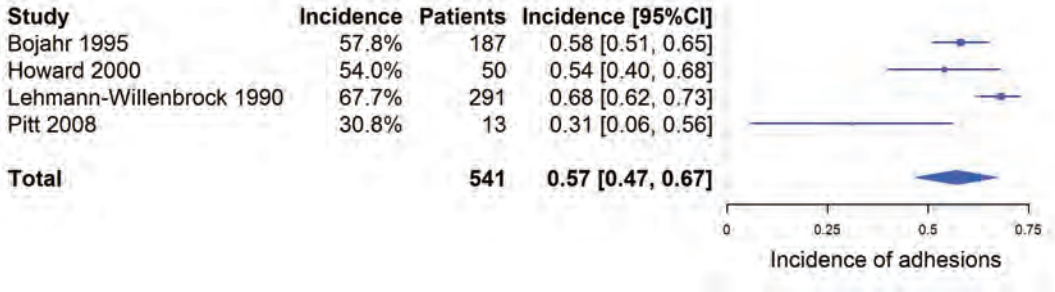

Figure 7 Forest plot of incidence of adhesions in patients with chronic postoperative pain, including all studies

Sensitivity analyses

Some sensitivity analyses slightly changed the point estimate, but in none of these analyses was the change clinically relevant. No other sensitivity analyses changed our results. Studies with a high risk of bias presented a significantly lower incidence of adhesive small bowel obstruction (1.5%, 0.9% to 2.0%). The incidence of adhesive small bowel obstruction was comparable to the presented estimates in studies with low and intermediate risk of bias.

Discussion

The results of this study show that adhesion formation has a large negative effect on patients' health and is associated with an increased workload in clinical practice. Many patients develop an episode of small bowel obstruction or require emergency surgery with adhesiolysis for small bowel obstruction. Adhesiolysis in repeat surgery is associated with an increased incidence of inadvertent bowel injury and increases the operating time. Other

sequelae of adhesion formation are decreased pregnancy rates, increased fertility treatments, and chronic abdominal pain. Considerable heterogeneity of studies was present.

Strengths and limitations of study

The major strengths of this review are the systematic approach and the large number of studies included. We have provided a comprehensive assessment of the burden of adhesions that is relevant to both clinicians and patients. The collected data present a good overview of the burden of adhesions at a population level, and the results were robust in extensive sensitivity and subgroup analyses.

Some potential limitations should be discussed. Firstly, the results should be interpreted with caution as we found considerable heterogeneity. Local variations in operative techniques, environmental factors, and the case mix seem to influence the incidence of adhesion related complication.

Secondly, publication bias cannot be excluded, as we found asymmetry in some funnel plots. Part of this asymmetry is explained by clinical heterogeneity between the patient groups included in different studies rather than by publication bias. Some asymmetry, however, is due to high incidences derived from high quality studies designed to assess incidences of small bowel obstruction or enterotomy.(5;10;14;18;19) That is, some smaller low quality studies reporting lower incidences were possibly not identified. Our sensitivity analyses, however, showed that our results were quite robust, so we do not expect that these smaller low quality studies would change our results.

Thirdly, we excluded studies done before 1990, which might have introduced bias. We believe, however, that studies done before 1990 would not provide an estimate that is generalisable to current practice because of the broad introduction of laparoscopy in general surgery at that time and the increased use of tissue sparing techniques and instruments at the end of the 20th century. Furthermore, sensitivity analyses did not show relevant differences between the period before and after 2000, suggesting that we could combine the data from the studies of the past two decades to provide a more precise estimate.

Fourthly, about 4% of papers could not be retrieved. We tried to retrieve these papers by contacting editors, authors, and other libraries in the Netherlands and abroad. The studies that could not be retrieved were small case series. The robustness of our sensitivity analyses shows that that these small case series would be unlikely to have changed our results.

Fifthly, costs and quality of life implications are not included in our analyses as these were either not reported at all or reported in such a heterogeneous way that pooling was not possible. On the basis of the high incidences of adhesion related complications, adhesions might affect the quality of life in many patients and cause a significant economic burden.

Comparison with other studies

The landmark publications of the SCAR Group were the first to consider the effect of postoperative adhesion formation in a large population.(4;15;16) In the SCAR studies, readmissions (defined by identification and diagnostic codes) were used as a proxy for the effect of adhesions. Incidence of adhesions will be difficult to confirm using these diagnostic codes. In the SCAR studies, many readmissions were classified as possibly related to adhesions that could not directly be linked to adhesions. Our study is unique in presenting distinct complications from adhesions as outcomes. Such outcomes are more interpretable for

clinicians and patients. Additionally, the large number of studies included in our analysis represented a fivefold higher number of patients than in the SCAR studies, and our results are more complete in analysing adhesion related complications, such as infertility and chronic pain, which in general do not require readmission.

The differences in incidences between laparoscopy and open surgery in this review are in agreement with an earlier study from our group, which showed small benefits of laparoscopy on adhesion related outcomes.(20) The results of this study contribute to the existing evidence that laparoscopy reduces the incidence of adhesion related complications. Notably, laparoscopy does not totally prevent adhesion formation, contradicting the opinion that the use of anti-adhesive barriers is not needed in laparoscopy.(7)

Implications for clinical practice

We have shown that postsurgical adhesion formation has an important risk for morbidity. The complications related to adhesions are diverse in nature and clinical consequences, varying from emergency reoperations for small bowel obstruction to fertility treatments. Informing patients about these risks before abdominal surgery is imperative. Failure to do so could result in medicolegal claims.(21) However, less than 10% of surgeons and gynaecologists routinely inform their patients of the risks of adhesions.(7;9)

This study provides important data for the development of guidelines for prevention of adhesions. So far, guidelines are present only in gynaecology, which comprises a minority of adhesion related problems in comparison with general surgery, particularly gastrointestinal and paediatric surgery.(22) Our review shows important relations between type of surgery and incidence of adhesion related complications. Evidence shows that adhesion barriers effectively reduce adhesion formation in high risk surgery.(13;23;24) The detailed knowledge of the disease burden of adhesions now available may be used to power future trials of anti-adhesive barriers preventing clinically relevant outcomes of adhesions.

Conclusions

This review provides detailed and systematically analysed knowledge of the large disease burden of adhesions. Complications of postoperative adhesion formation are frequent, have a large negative effect on patients' health, and increase workload in clinical practice. Many patients develop an episode of small bowel obstruction or an inadvertent bowel injury due to adhesiolysis. The quantitative effects should be interpreted with caution owing to large heterogeneity.

What is already known on this topic

Adhesion formation is a common cause of long term complications following abdominal or pelvic surgery

Adhesion related complications comprise various clinical entities including small bowel obstruction, female infertility, difficulties at reoperation, and chronic pain

The incidence and effect of adhesion related complications are not precisely known

What this study adds

Detailed and systematically analysed knowledge of the large disease burden of adhesions is now available

This knowledge may be used for better preoperative patient counselling and operative management and to power future trials of anti-adhesive barriers

Studies on adhesion formation and its clinical consequences are heterogeneous

Acknowledgments

We thank I Gerych, General Surgery Department, Danylo Halytsky Lviv National Medical University, Ukraine, for his help in translating articles written in Russian.

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PART I: Awareness of adhesion related complications

Chapter 3: Adhesion awareness: a national survey of surgeons

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Published in: World Journal of Surgery. 2010;34;2805-12

Abstract

Background

Postoperative adhesions are the most frequent complication of abdominal surgery, leading to high morbidity, mortality, and costs. However, the problem seems to be neglected by surgeons for largely unknown reasons.

Methods

A survey assessing knowledge and personal opinion about the extent and impact of adhesions was sent to all Dutch surgeons and surgical trainees. The informed-consent process and application of antiadhesive agents were questioned in addition.

Results

The response rate was 34.4%. Two thirds of all respondents (67.7%) agreed that adhesions exert a clinically relevant, negative effect. A negative perception of adhesions correlated with a positive attitude regarding adhesion prevention ($p = 0.182$, $p < 0.001$). However, underestimation of the extent and impact of adhesions resulted in low knowledge scores (mean test score 37.6%). Lower scores correlated with more uncertainty about indications for antiadhesive agents which, in turn, correlated with never having used any of these agents ($p = 0.140$, $p = 0.002$; $p = 0.095$, $p = 0.035$; respectively). Four in 10 respondents (40.9%) indicated that they never inform patients on adhesions and only 9.8% informed patients routinely. A majority of surgeons (55.9%) used antiadhesive agents in the past, but only a minority (13.4%) did in the previous year. Of trainees, 82.1% foresaw an increase in the use of antiadhesive agents compared to 64.5% of surgeons ($p < 0.001$).

Conclusions

The magnitude of the problem of postoperative adhesions is underestimated and informed consent is provided inadequately by Dutch surgeons. Exerting adhesion prevention is related to the perception of and knowledge about adhesions.

Introduction

Postoperative adhesions occur in about 90% of all patients undergoing abdominal surgery and lead to at least one readmission for a third of these patients in the following 10 years (1; 2). Adhesions become clinically apparent in the form of chronic abdominal pain, female infertility, and small-bowel obstruction (3; 4). Furthermore, adhesions can seriously complicate subsequent surgery (5; 6). Therefore, postoperative adhesions should not merely be regarded as a side effect of abdominal surgery but as the most common complication caused by abdominal surgery.

Regardless of an open or a laparoscopic approach, the surgical treatment of adhesions induces the reformation as well as new formation of adhesions (7; 8). Hence, adhesion prevention is of key importance. For obvious reasons, reducing surgical trauma by meticulous surgical technique is the primary step that needs to be exerted at all times. However, performing surgery implies surgical trauma to some extent but it can be further reduced by other means, e.g., using powder-free gloves, wetting tissues, and reducing operative time (9). The use of adhesion barriers seems inevitable to obtain further adhesion prevention. A local barrier composed of hyaluronic acid and carboxymethylcellulose (Seprafilm®, Genzyme, Cambridge, MA, USA) has proven effective in reducing adhesions in various open general surgery studies (10). Previous reviews have also shown significant benefit with the use of Interceed® membrane (Ethicon 360, Johnson & Johnson, New Brunswick, NJ, USA), composed of oxidized regenerated cellulose, in open gynaecologic surgery (11). Administration of an icodextrin solution (Adept®, Baxter Healthcare Corp., Deerfield, IL, USA) that spreads throughout the peritoneal cavity has shown adhesion reductive capacity in benign laparoscopic gynaecologic surgery (12).

In contrast to most surgical complications, the risk of adhesion-related morbidity remains for many years and complications are often not followed up by the primary surgeon. In addition, symptoms of adhesion-related complications vary and a fully effective remedy has not yet been discovered. All these factors have probably resulted in an undervaluation of postoperative adhesions by surgeons. This in turn explains why adhesions are mentioned only sporadically during the informed-consent process (13; 14). Nevertheless, failure to do so can be regarded as an omission of the doctor's duty of care and has already resulted in successful negligence claims (15).

In spite of the extent and impact of postoperative adhesions, we are under the impression that surgeons lack sufficient awareness about this most common complication. Moreover, they seem to provide inadequate informed consent on and take insufficient preventive actions against adhesions. However, until now, no data has been available to substantiate these assumptions. Therefore, we conducted a nationwide survey assessing the awareness of and behaviour toward adhesions among Dutch surgeons and surgical trainees.

Materials and methods

Design of the survey

A steering group of 11 general and gynaecologic surgeons with a special interest in adhesions and its associated morbidity (Dutch Adhesion Group) conceived a first set of survey questions. These questions were edited by two independent researchers, both experts

in survey and multiple-choice test construction. Subsequently, five surgeons and three surgical trainees tested the survey for indistinctness and leading questions. After making adjustments, the survey was reviewed again and consecutively approved by the steering group, the independent researchers, and the test group of surgeons and trainees. The survey consisted of 55 multiple-choice questions, four open-ended questions, and four optional questions with a total word count of 716. In its final layout, both an electronic online version (six web pages) and a printed version (three pages) were available in Dutch (see Appendix for a translated version).

Knowledge test

Eight multiple-choice questions concerning the prevalence and morbidity of adhesions were formulated based on up-to-date and best-available evidence. The following statements were considered correct:

Approximately 70% of small-bowel obstructions are due to postoperative adhesions (16–18).
The 5-year readmission rate after operative procedures of the colon or rectum directly related to postoperative adhesions is approximately 5% (19–21).
The 10-year readmission rate after any abdominal surgery probably or directly related to postoperative adhesions is approximately 30% (1; 2).
Inadvertent enterotomy during adhesiolysis occurs in 20% of patients with a history of abdominal surgery (5; 6).
A total colonic resection has the highest risk of adhesion-related morbidity compared with a partial small-bowel resection, an appendectomy, or a resection of the rectum (2; 21).
Age above 60 years is associated with fewer adhesions, a history of abdominal surgery with more adhesions, and a history of Crohn's disease with no difference in adhesion formation (2; 21).

Survey distribution

We aimed to distribute the survey among all officially registered Dutch surgeons and trainees (n = 1 282 and 432, respectively). Contact details were retrieved from the 2008 annual report of the Dutch Association for Surgery from the section of regular members (n = 1 009) and members of the association of surgical trainees (n = 446). We approached the surgeons and trainees by electronic mail (e-mail) or by postal mail when no or no valid e-mail address was available. A personalized mail was sent on Tuesday (at 6:00 a.m. in case of e-mail) and a reminder sent the next Tuesday (at 7:00 p.m. in case of e-mail) when no response was recorded yet. As an incentive, five portable audio players and 40 pens with inbuilt laser pointer and USB stick were raffled among all respondents. The survey closed 3 weeks after the first mailing.

Data analysis

Only surveys more than 80% complete, excluding optional questions, were included. We defined subgroups of respondents as trainees, general surgeons, gastrointestinal surgeons, or other surgeons. Proportions were compared using $\chi 2$ tests. Comparisons between groups were performed using the Mann–Whitney U test, the Wilcoxon signed-rank test, or the Kruskal–

Wallis test with post-hoc Bonferroni correction. Knowledge test scores were compared with Student's t tests and ANOVA with post-hoc Bonferroni correction. Correlations were calculated using Spearman's rank correlation and a $p < 0.050$ was considered significant. Statistics were performed using SPSS® version 15.0 (SPSS, Inc., Chicago, IL, USA).

Results

A total of 1 455 surgeons and trainees were contacted by e-mail (83.8%) or postal mail (16.2%). Twenty-three physicians indicated not to participate. After 1 week, 352 surveys were collected, and there were 523 surveys at close of the survey. Of these, 22 incomplete surveys (4.2%) were rejected, resulting in a response rate of 34.4% (501 surveys, 98% complete) representing 90.7% of all Dutch surgical departments (98.3% of all teaching and 81.3% of all nonteaching departments). Response rates were comparable for e-mail and postal mail (35.3 vs. 29.8%, respectively, $p = 0.102$), but higher for surgeons than for trainees (Table 1). The survey was completed by a comparable number of trainees (n = 131), general surgeons (n = 130), gastrointestinal surgeons (n = 116), and other surgeons (n = 124) ($p = 0.767$).

Table 1 Respondents (n = 501)

	Trainees	Surgeons	p Value
Response rate (%) (n)	29.4% (131 of 446)	36.7% (370 of 1 009)	0.007
Experience, mean (SD) (years)	4.3 (1.6)	13.2 (9.6)	n.a.
Full-time employment (%) (n)	89.9% (116)	88.8% (316)	0.718
Academic hospital employment (%) (n)	33.6% (44)	25.8%(95)	0.088

SD standard deviation; n.a. not applicable
All $\chi 2$ tests

Opinion on adhesions

About two thirds (67.7%) of all respondents agreed that adhesions exert a clinically relevant and predominantly negative effect. The proportion was significantly higher for trainees than for surgeons (75.6 vs. 64.9%, respectively, $p = 0.025$). A small group (6.0%) indicated that adhesions exert a clinically relevant and predominantly positive effect. Half of all respondents (50.6%) considered adhesiolysis for treating pain not effective, whereas 26.2% considered it effective.

Awareness of adhesions and their associated morbidity

Respondents scored a mean of 37.6% correct answers on the knowledge test, with trainees scoring slightly but significantly higher than general surgeons (39.9 vs. 34.6%, $p = 0.032$). Only 6.9% of respondents reported a correct 10-year readmission rate after abdominal surgery probably or directly related to adhesions (30%), whereas 69.0% thought it was 10% or lower. Also, 62.9% underestimated the percentage of small-bowel obstructions caused by adhesions, reporting a percentage of 50% or lower. On the other hand, a vast majority of respondents (87.6%) correctly indicated that a history of abdominal operations is associated with increased adhesion-related morbidity. The knowledge test score did not correlate with respondents' opinion on adhesions ($p = 0.010$, $p = 0.830$).

Informed consent

One in 10 respondents (9.8%) reported that they routinely include adhesions or related morbidity in the informed consent information for both laparotomies and laparoscopies. Yet, 40.9% of all respondents reported that they never mention it at all (Fig. 1). No correlation was observed with opinion on adhesions or knowledge test score ($p = 0.031$, $p = 0.497$; $p = 0.016$, $p = 0.730$; respectively). Trainees and nonacademic surgeons provided adhesion information during informed consent less often than surgeons and academic surgeons, respectively (both $p = 0.002$). Furthermore, providing information on adhesions before a laparoscopic procedure was done less often in comparison with laparotomy ($p < 0.001$). Informing fewer patients before a laparoscopy correlated with a greater belief that laparoscopy is a means to limit adhesion formation ($p = 0.186$, $p < 0.001$).

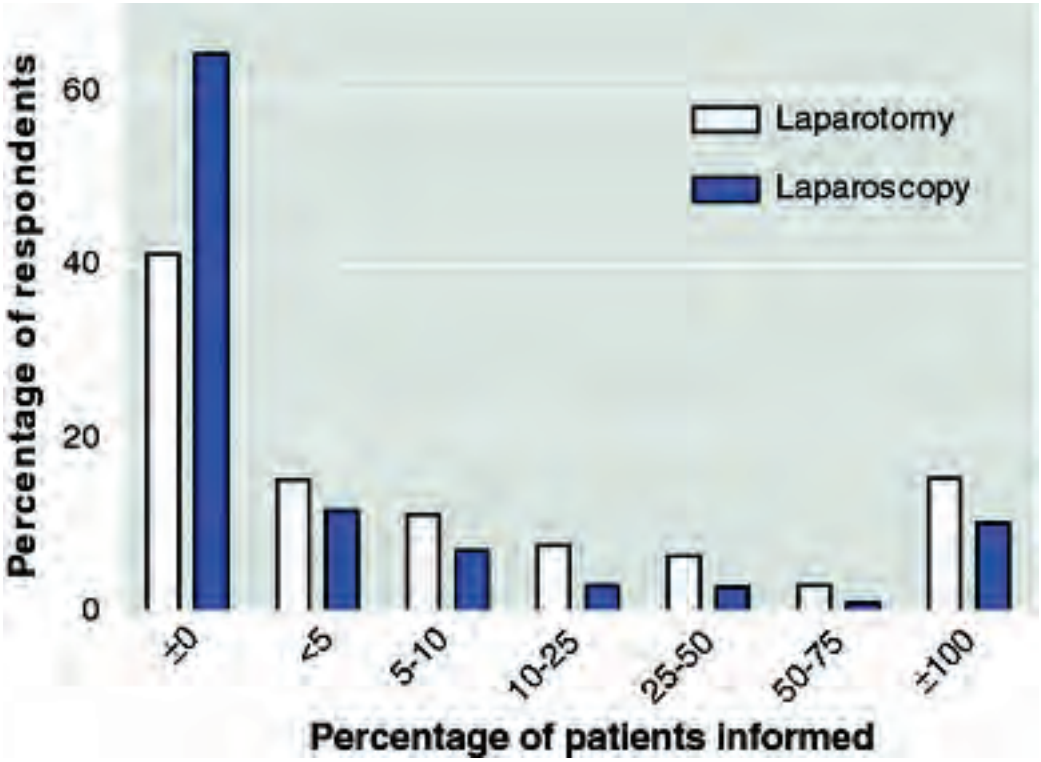

Figure 1 Informed consent

Adhesion prevention

Four in 10 respondents (39.1%) expressed a positive opinion on adhesion prevention, 22.4% expressed a negative one. In addition, a positive opinion correlated with a negative view of adhesions ($p = 0.182$, $p < 0.001$). All respondents, except gastrointestinal surgeons, believed more strongly in adhesion prevention for specific indications than for all abdominal surgery ($p < 0.001$). Significantly more surgeons than trainees believed that a meticulous surgical technique minimizes adhesions (83.5 vs. 65.6%, $p < 0.001$). Similarly, significantly more gastrointestinal than nongastrointestinal surgeons believed that laparoscopy reduces adhesion formation (90.5 vs. 72.0%, $p < 0.001$) (Fig. 2).

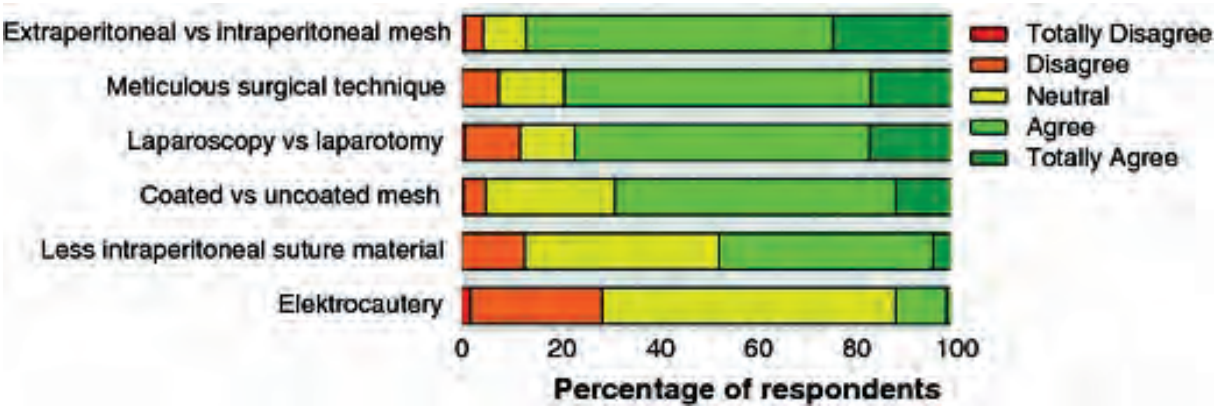

Figure 2 Techniques to minimize adhesions

Antiadhesive agents

Of all respondents, 26.5% expressed a positive attitude toward antiadhesive agents and 29.1% expressed a negative one (Fig. 3). Although a majority of surgeons (55.9%) had used at least one of these agents, only a minority did in the previous year (13.4%). Significantly higher proportions of gastrointestinal and academic surgeons used an antiadhesive agent in the previous year compared to general and nonacademic surgeons, respectively (23.0 vs. 9.0%, $p = 0.001$; 23.9 vs. 10.5%, $p < 0.0001$; respectively). Not using antiadhesive agents any longer showed no significant associations with knowledge test score, opinion on adhesions, adhesion prevention, or antiadhesive agents ($p = 0.622$, $p = 0.431$, $p = 0.283$, $p = 0.209$, respectively). Most surgeons used Adept® (8.9% ever, 8.5% last year) and Seprafilm® (33.7% ever, 5.4% last year). In the group of surgeons who used antiadhesive agents, 78.8% did so in adhesion-related laparotomies, 29.2% in abdominal wall surgery, and 21.8% in (sub)total colectomies. In general, use of products for high-risk operations regarding adhesion formation was higher than for low-risk operations ($p < 0.001$). Uncertainty about when to use these products correlated with never having used any products ($p = 0.095$, $p = 0.035$) and lower knowledge test scores ($p = 0.140$, $p = 0.002$).

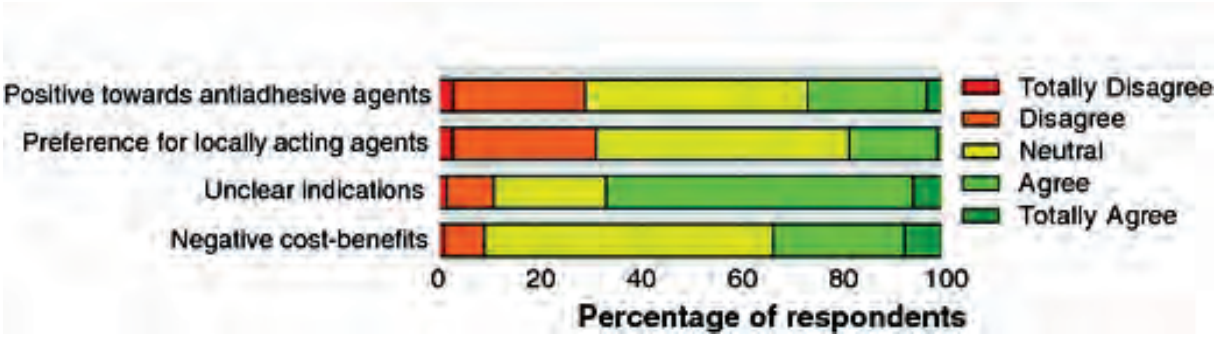

Figure 3 Opinion on antiadhesive agents

Of all trainees, 82.1% predicted that the use of antiadhesive agents will increase compared with 64.5% of all surgeons ($p < 0.001$). Such opinion correlated with a negative view of adhesions ($p = 0.141$, $p = 0.002$) and with a more positive view in terms of cost–benefits ($p =$

0.148, p = 0.001). Most respondents anticipated that new antiadhesive agents would come to the market and that the evidence either for or against adhesion prevention would increase.

Discussion

Adhesions and related complications lead to substantial morbidity and mortality, with increased medical costs (22; 23). This nationwide survey shows that two of three Dutch surgeons recognize adhesions as a clinically relevant and negative entity. However, readmission rates and small-bowel obstructions caused by adhesions are heavily underestimated. Moreover, the informed-consent process and application of antiadhesive agents are not in line with the extent and impact of postoperative adhesions. Therefore, it can be concluded that the knowledge and awareness of and the behaviour toward adhesions is limited among Dutch surgeons and surgical trainees.

At least 40% of respondents did not inform any patients about postoperative adhesions or related morbidity and only very few informed patients routinely. This corresponds with the recent finding that more than 90% of consent forms lack this information (13). In contrast, the risks for hemorrhage and infection after abdominal surgery are almost invariably discussed during the informed-consent process. Adhesion-related complications share nearly all features of these complications, including the risk of death, but may occur many years after the operation. Thus, it is essential to discuss adhesions as a possible complication during the informed-consent process. In addition, in case of any reoperation, a high risk of inadvertent organ damage exists and should be discussed prior to surgery as well. These recommendations apply also for laparoscopic procedures since laparoscopy has not been proven to reduce adhesion-related morbidity compared with laparotomy, though definite studies are lacking (24).

Current surgical trainees consider adhesions a negative drawback of surgery more often, have a slightly better understanding of the extent of the problem, rely less on surgical technique to reduce adhesions, and have a higher belief in an increasing use of antiadhesive agents, compared to surgeons. In contrast, they seem to inform fewer patients about adhesions or adhesion-related morbidity compared to current surgeons. The reason for this is unclear, but this behaviour may change when they have more responsibilities and follow-up their own patients more closely. The finding is of interest for the future and might mandate (educational) interventions with this group of young surgeons before they face legal claims. The significantly lower response rate of surgical trainees compared to surgeons can be explained by the higher number of trainees' contact details than the number of officially registered trainees for general surgery. This is probably due to the fact that plastic and orthopedic surgery trainees share the first 2 years of training.

The current study is the first to evaluate awareness and behaviour of surgeons regarding adhesions. Recently, two similar studies reported on adhesion awareness among gynecologic surgeons in the United Kingdom and Germany (14; 25). Little over half of those respondents agreed that adhesions are the most common complication after abdominal surgery. This is in line with our finding that the impact of adhesions is underestimated. Yet, around three in four gynecologic surgeons indicated that they inform patients routinely about adhesions and about half of the respondents stated that they use antiadhesive agents regularly. This clearly surpasses the current behaviour of Dutch surgeons and reflects a higher awareness of

adhesions among gynecologic surgeons. Nevertheless, the 8.8% response rate of the British gynecologists and the 33.5% response rate of German gynecologic departments might reflect a selection bias.

Approximately 80% of respondents agreed that an extraperitoneal mesh, meticulous surgical technique, and laparoscopy reduce adhesions. Only a quarter of surgeons expressed a positive opinion toward antiadhesive agents. In addition, only one in 10 surgeons used an agent in the past year, with Adept® taking a small lead over Seprafilm®. Adept® is a liquid acting throughout the whole abdomen; Seprafilm® is a site-specific barrier film. The efficacy of Seprafilm® has already been evidenced in general surgery, whereas for Adept® efficacy has been shown in laparoscopic gynecologic surgery and results in general surgery are awaited (10; 12). Both agents have been shown to be safe in general abdominal surgery, though application of Seprafilm® on bowel anastomoses should be avoided (10; 26; 27). Although current agents do not provide complete prevention of postoperative adhesions, it is worth considering their use in high-risk surgery such as colorectal procedures. Even a relative decrease in adhesions might entail benefits for the patient and the surgeon. Interestingly, uncertainty about indications for antiadhesive agents was correlated with never having used any agents and with lower knowledge scores.

This study demonstrates that a change in behaviour is needed among surgeons and trainees. Patients have to be informed of the risks of adhesions routinely and the application of clinically available antiadhesive agents should at least be considered in specific abdominal surgery (28). However, to obtain changes in behaviour, both knowledge and attitudes have to be addressed (29). Barriers for improving knowledge include accessibility and volume of information; attitudes can be affected by a lack of agreement or poor methodology in evidence, but also by personal beliefs and experiences. Therefore, attempts to obtain sustainable changes in behaviour have to target multiple aspects. Moreover, breakthrough results from basic research should be translated to clinically applicable agents (30).

Some limitations of this study should be noted. First of all, the 34.4% response rate might reflect a selection bias, possibly providing more positive results. Furthermore, no elaborate nonresponse analysis could be performed due to the lack of any central database comprising detailed information on Dutch surgeons. On the other hand, responses were recorded from 90.7% of all Dutch surgical departments. In addition, response rates were markedly higher than in the recent survey among gynecologic surgeons in the UK and a survey in the USA on work, stress, and research among academic surgeons (8.8 and 22.7%, respectively) (14; 31). Our relatively high response rate might be due to the raffle, which is known to increase response rates without affecting response quality (32; 33).

The knowledge test was based on up-to-date and best-available evidence selected by the steering group of general and gynecologic surgeons. Several rounds of pilot testing were conducted to ensure comprehensibility and face and content validity of the survey. However, although most of the knowledge questions were based on very large cohort studies, some still consider the consistently found high morbidity controversial. Yet, even if the true morbidity would be lower, many of the respondents would still underestimate the magnitude of the problem.

Finally, this study surveyed only Dutch surgeons and surgical trainees, but results are likely to be generalizable to surgeons worldwide; adhesions are encountered after all

abdominal surgeries and the associated morbidity, mortality, and costs are comparably high in different countries (23; 34; 35).

As for the future, action must be taken to improve knowledge, attitude, and behaviour concerning adhesions among Dutch surgeons and surgical trainees. Specialty courses could be developed and rewarded credits; compulsory classes on adhesions and antiadhesive agents should be embedded in the surgical training program. Nonetheless, surgeons represent only one of the many parties involved in adhesion awareness. Attention must also be given to the other specialists operating in the abdominal cavity, patients, hospitals, antiadhesive agents manufacturers, and health insurance companies in order to improve awareness of and behaviour toward adhesions. In order to follow-up on the actions, the results of this survey can serve as a benchmark for later research.

Acknowledgments

The Dutch Adhesion Group consists of Mrs. E. A. Bakkum (gynecologic surgeon, Amsterdam), Mrs. N. D. Bouvy (surgeon, Maastricht), F. P. Dijkhuizen (gynecologic surgeon, Arnhem), H. van Goor (surgeon, Nijmegen), F. W. Jansen (gynecologic surgeon, Leiden), J. Jeekel (surgeon, Rotterdam), R. F. Kruitwagen (gynecologic surgeon, Maastricht), M. M. Reijnen (surgeon, Arnhem), E. J. van Santbrink (gynecologic surgeon, Rotterdam), D. J. Swank (surgeon, Gouda), and Mrs. G. C. Trimbos-Kemper (gynecologic surgeon, Leiden).

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PART I: Awareness of adhesion related complications

Chapter 4: Comparison of operative notes with real-time observation of adhesiolysis-related complications during surgery

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Published in: British Journal of Surgery 2013;258(1);98-106

Abstract

Background
The operative report contains critical information for patient care, serves an educational purpose and is an important source for surgical research. Recent studies demonstrate that operative reports are unstructured and lack vital components. The accuracy of the operative notes has never been assessed. The aim of this study was to analyse the accuracy of operative reports by comparing notes with intraoperative observer-derived findings regarding adhesions and adhesiolysis-related complications.
Methods
The incidence of adhesions and adhesiolysis-induced injury were scored from the reports by a researcher blinded to operative findings obtained prospectively by direct observation. In addition, factors influencing correct reporting were analysed, including sex, surgical experience, delay in dictation, and the gradual introduction of a new report template with a focus on describing operative findings rather than actions taken.
Results
A total of 755 consecutive operative reports were analysed. Sensitivity and specificity for the incidence of adhesions was 85.1 and 72.4 per cent respectively. Six of 43 inadvertent enterotomies, and 17 of 48 other organ injuries, had not been reported. All missed bowel injuries were found in reports written in the old template. A median delay in dictating of 3(range 1–226) working days was found for 56 reports (7.4 per cent). Documentation of inadvertent enterotomies was missing more often in delayed reports (2 of 3 *versus* 4 of 40 in reports dictated with no delay; P=0.022).
Conclusion
The sensitivity and specificity of operative reports noting adhesions and adhesiolysis were low. One in seven enterotomies was not reported. Effort should be put into teaching timely, meaningful, structured and accurate reporting of surgical procedures.

Introduction

An operative report is the official medical documentation of an operation. A high accuracy in the report is mandatory as it contains crucial information for lifelong safe patient care. Reports need to be accurate for proper billing and to provide valuable information during medicolegal procedures. In addition, an operative report is an important tool for education and a source for clinical research.(1-3)

Recent studies have raised serious questions about the completeness of an operative report.(1-5) In one study, a fundamental element such as the name and signature of the surgeon was either not stated or was unclear in 15 per cent of reports.(2) Another study found that basic postoperative instructions concerning antibiotics and thrombosis prophylaxis were lacking in 85 and 86 per cent of reports respectively.(1) The reports improved after the introduction of a standard operative report sheet.(1) Reports on cholecystectomies often lack description of the key procedural steps taken during the operation, such as the critical view of safety.(3;5;6)

Little is known about the accuracy of the information written in operative reports.(7) For laparoscopic procedures, videotaping of the procedure can support a written report and increase accuracy. The videotape may even replace the report, although viewing the video is more time consuming than reading a report.(8) For open procedures, video recording is much more complicated and often not complete. To date, no comparison between operative report notes and the actual findings and actions taken during open surgery has been performed.

The aim of this study was to assess the accuracy of information recorded in operative reports. Adhesiolysis-induced injuries noted in the operative report were chosen for comparison because of their clinical relevance.(9)

Methods

Between June 2008 and June 2010, a researcher observed closely all elective abdominal operations at Radboud University Nijmegen Medical Centre; the researcher was present in the operating room but did not take part in the operation. Detailed information on adhesiolysis and iatrogenic organ injury was noted as part of a study investigating the impact of adhesions on operative outcome.

The reports of 755 consecutive operations included in the LAParotomoy or LAParoscopy and ADhesiolysis (LAPAD) study (clinicaltrials.gov registration number NCT01236625) were the basis for this study. The LAPAD study was designed to assess the incidence of adhesions and impact of adhesiolysis on operative and postoperative complications, quality of life and socioeconomic costs. Details of the LAPAD study have been described elsewhere.(10)

During surgery, detailed information concerning adhesions, adhesiolysis and inadvertent organ damage was collected through direct observation by a trained researcher. Surgeons performing the operations were aware of the study details and that operative data were collected. Data from operative reports were extracted by a trained researcher, who was blinded for the results of the LAPAD study and was not involved in patient care during the study period.

Variables

The sensitivity and specificity of operative reports regarding the incidence of adhesions were calculated. For this purpose, operative reports with explicit documentation of adhesions, or synonyms thereof, or notes probably indicating the presence of adhesions were scored as positive. Examples of terms probably indicating adhesions were: ‘grown together’ or ‘frozen together’, in addition to reports of the dissection of structures that are normally not attached to one another. Operative reports explicitly stating that the abdomen was free from adhesions, or that did not note any adhesions, were scored as negative. With regard to the incidence of adhesiolysis, the sensitivity and specificity of an operative report for dissecting adhesions were determined.

Classification of enterotomies

Where an enterotomy had occurred during adhesiolysis, an analysis was made of cases where an enterotomy was noted explicitly in the operative report, phrases that possibly indicated an enterotomy (for example, ‘a bowel hole was sutured’) or where there was no mention of any enterotomy. Over-reporting of organ injury was not analysed to determine an incorrect notation, because this possibility had been taken into account within the definition of inadvertent enterotomy. In the LAPAD database, only enterotomies that were made accidentally were registered as inadvertent enterotomies. Documentation of an enterotomy when dissecting a bowel loop with a pre-existing fistula, and enterotomies necessary to obtain an oncological resection, were not registered as an enterotomy in the LAPAD database. Notes on seromuscular and other organ injuries were also compared with real-time observations.

Surgeon characteristics and the report template

In a second analysis, surgeon and surgery-related characteristics that might impact on the correct reporting of adhesions and adhesiolysis were evaluated. Surgeon characteristics were: sex, surgical experience (consultant or resident), report template (old or new) and delay before dictating the report. For residents, their year of training, initial teaching hospital, and duration of training at the authors’ academic centre and previously in a teaching hospital were also analysed. Interactions between surgeon characteristics were explored and statistically significant interactions reported.

During the study period, a new operative report template was gradually implemented that emphasized the operative findings while limiting the reporting of the actions taken. The old report template included text fields for patient and surgeon data, operative codes, a summary text field and a free text field with the subheading ‘operative procedure’. The new report template included all fields from the old template, and the subheadings ‘preparation’ and ‘operative findings’ were added to the free text field. As a rule, operative reports in the authors’ institution are dictated immediately after surgery. Later dictations were regarded as delayed. Surgery characteristics were previous abdominal surgery, enterotomies and adhesiolysis time. Factors included in a final analysis that potentially could affect correct reporting of enterotomies were the report template, delayed dictation, surgeon’s sex and surgical experience.

Statistical analysis

Comparison between groups were conducted using an unpaired t test for normal distributed continuous data, ANOVA in not normal distributed continuous data and the $\chi 2$ test for dichotomous data. SPSS® for Windows® version 16.0 software (IBM, Armonk, New York, USA) was used for statistical analysis, with $P<0.050$ considered significant.

Results

All 755 operative reports were retrieved. The new report template was used in 128 reports (17.0 per cent). Fifty-six reports (7.4 per cent) were dictated at a later time, with a median delay 3 (range 1–226) working days. Some 690 (91.4 per cent) of the reports were written by male surgeons. Consultants wrote 415 (55.0 per cent) of the reports, and residents wrote 340 (45.0 per cent). Inadvertent enterotomy occurred in 43 operations (5.7 per cent). Seromuscular and other organ injuries occurred in 142 (18.8 per cent) and 48 (6.4 per cent) operations respectively.

Incidence of adhesions

Absence of adhesions was reported explicitly in only nine reports; two of these patients actually had adhesions. In 284 reports (37.6 per cent) no notation had been made for the presence or absence of adhesions. The presence of adhesions was reported explicitly in 450 reports (59.6 per cent) and probably in 12 (1.6 per cent). Thus, 293 (38.8 per cent) were scored as negative for adhesions and 462 (61.2 per cent) as positive. The incidence of adhesions found by the observer was 497 (65.8 per cent) of 755. The sensitivity and specificity for the incidence of adhesions were 85.1 and 72.4 per cent respectively. Operative reports were correct regarding the incidence of adhesions in 79.2 per cent of cases.

Performance of adhesiolysis

Thirty-nine reports (5.2 per cent) explicitly stated that no adhesiolysis had been performed; in seven of these cases, adhesions had been cut according to the observer notes. No documentation of adhesiolysis was found in 325 reports (43.0 per cent); in 112 (34.5 per cent) of these adhesiolysis had been performed. Performance of adhesiolysis was reported explicitly in 376 reports (49.8 per cent) and probably in 15 (2.0 per cent). The incidence of adhesiolysis by direct observation was 475 (62.9 per cent) of 755. The operative report was correct concerning adhesiolysis in 79.6 per cent, with a sensitivity of 74.9 per cent and a specificity of 87.5 per cent.

Iatrogenic injury during adhesiolysis

Enterotomies were noted explicitly in 37 reports, and possibly in 11. In nine of the explicitly and two of the possibly reported enterotomies, the bowel injury did not result from adhesiolysis according to the definition used in the LAPAD study. In six cases enterotomy occurred during dissection of fistulas, and in three as part of an oncological resection. In the remaining two cases there was no explanation for the discrepancy between the report and the observer notes.

Of 43 inadvertent enterotomies resulting from adhesiolysis, only 28 were reported explicitly, nine possibly, and no report of enterotomy was made in six cases. Seromuscular injury of the bowel was missing in the operative report for 54 (38.0 per cent) of 142 procedures. In 17 of 48 operations with iatrogenic injury to other organs, the following injuries were missing in the notes: liver injury (7), major vascular injury (3) and splenic injury (2).

Impact of surgeon and surgery characteristics on correct reporting

There was a significant interaction between surgical experience and surgeon's sex; thus sex was further analysed according to surgical experience. Most surgeon characteristics had no influence on the correct reporting of the incidence of adhesions, performance of adhesiolysis or inadvertent organ injury (Table 1). Of 340 reports written by residents, 38 (11.2 per cent) were by women. Female residents significantly underreported adhesiolysis compared with male residents (P=0.046). Residents initially trained in teaching hospital B produced incorrect reports more frequently for incidence of adhesiolysis than residents from the other teaching hospitals (P=0.019).

Table 1 Impact of surgeon characteristics on the correct reporting of adhesions and adhesiolysis

	Incidence of adhesions			Adhesiolysis		
	Correct (%)	Incorrect(%)	P-value	Correct (%)	Incorrect(%)	P-value
Report template						
• Old	492 (79)	135 (22)		499 (79.6)	128 (20.4)	
• New	106 (83)	22 (17)	.270	102 (79.7)	26 (20.3)	.979
Delay in dictation						
• Undelayed	554 (79)	145 (21)		547 (78.3%)	141(21.7%)	
• ≥ 2working days	44 (79)	12 (21)	.903	43 (76.8%)	43 (23.2%)	.587
Surgical experience						
• Consultant	328 (79)	87 (21)		325 (78.3)	90 (21.7)	
• Resident	270 (79)	70 (21)	.899	276 (81.2)	64 (18.8)	.331
Sex of consultant						
• Male	302 (78)	86 (22)		300 (77.3)	88 (22.7)	
• Female	26 (96)	1 (4)	**0.023**	25 (92.6)	2 (7.4)	.088
Sex of resident						
• Male	244 (81)	58 (19)		250 (82.8)	52 (17.2)	
• Female	26 (68)	12 (32)	0.075	26 (68.4)	12 (31.6)	**.046**
Length of training (years)						
• 1	1 (50)	1 (50)		2 (100.0)	0 (0.0)	
• 2	5 (83)	1 (17)		4 (66.7)	2 (33.3)	
• 3	19 (66)	10 (35)		21 (72.4)	8 (27.6)	
• 4	75 (80)	19 (20)		78 (83.0)	16 (17.0)	
• 5	99 (83)	20 (17)		96 (80.7)	23 (19.3)	
• 6	41 (86)	7 (15)		42 (87.5)	6 (12.5)	
• Fellow	30 (71)	12 (29)	.220	33 (78.6)	9 (21.4)	.621
Residents, duration of training in academic centre (months)*†	12 (1 - 32)	12 (1 - 32)	.361	12 (1 - 32)	10 (1 - 32)	.331 ¶
Residents, initial teaching hospital†‡						
• None	8 (67)	4 (33)	.215	10 (83.5)	2 (16.7)	.870
• A	60 (85)	11 (16)	.333	64 (90.1)	7 (9.9)	**.032**
• B	69 (76)	22 (24)	.173	67 (73.6)	24 (26.3)	**.019**
• C	36 (90)	4 (10)	.104	34 (85.0)	6 (15.0)	.545
• D	67 (80)	17 (20)	.832	68 (81.0)	16 (19.0)	.869

Values in parentheses are percentages unless indicated otherwise; *values are median (range). †Data from 298 operative reports made by residents (excluding fellows). ‡As well as an overall P value, results for residents in each centre were compared with those for all residents in the other centres. §$\chi 2$ test, except ¶ANOVA.

The reported incidence of adhesions and adhesiolysis was correct significantly more often when an enterotomy had been made or when the duration of adhesiolysis was long (P= 0.021 and P<0.001) (Table 2). Documentation of enterotomy was missing more often in reports

dictated following a delay and in those by female surgeons (Fig. 1). In the new report template, all enterotomies were noted.

Table 2 Impact of surgery characteristics on the correct reporting of adhesions and adhesiolysis

	Incidence of adhesions			Adhesiolysis		
	Correct (%)	Incorrect(%)	P-value	Correct (%)	Incorrect(%)	P-value
Abdominal surgery in history - No - Yes	 202 (79.8) 396 (78.9)	 51 (20.2) 106 (21.1)	 .759	 201 (77.9) 400 (80.5)	 57 (22.1) 97 (19.5)	 .405
Enterotomy made - No - Yes	 558 (78.4) 40 (93.0)	 154 (21.6) 3 (7.0)	 .021	 561 (78.8) 40 (93.0)	 151 (21.2) 3 (7.0)	 **.025**
Adhesiolysis time (minutes)* † - Adhesions/ Adhesiolysis not reported - Adhesions/ Adhesiolysis reported	 0 (0 - 0) 25 (0 - 177)	 5 (0 - 75) 0 (0 - 0)	 <.001 <.001	 0 (0 - 0) 26 (1 - 177)	 5 (1 - 75) 0 (0-0)	 <.001 <.001

Values in parentheses are percentages unless indicated otherwise; *values are median (range). †Data from 471 operations with adhesiolysis and known duration of adhesiolysis (duration missing in 4 patients). ‡$\chi 2$ test, except §ANOVA.

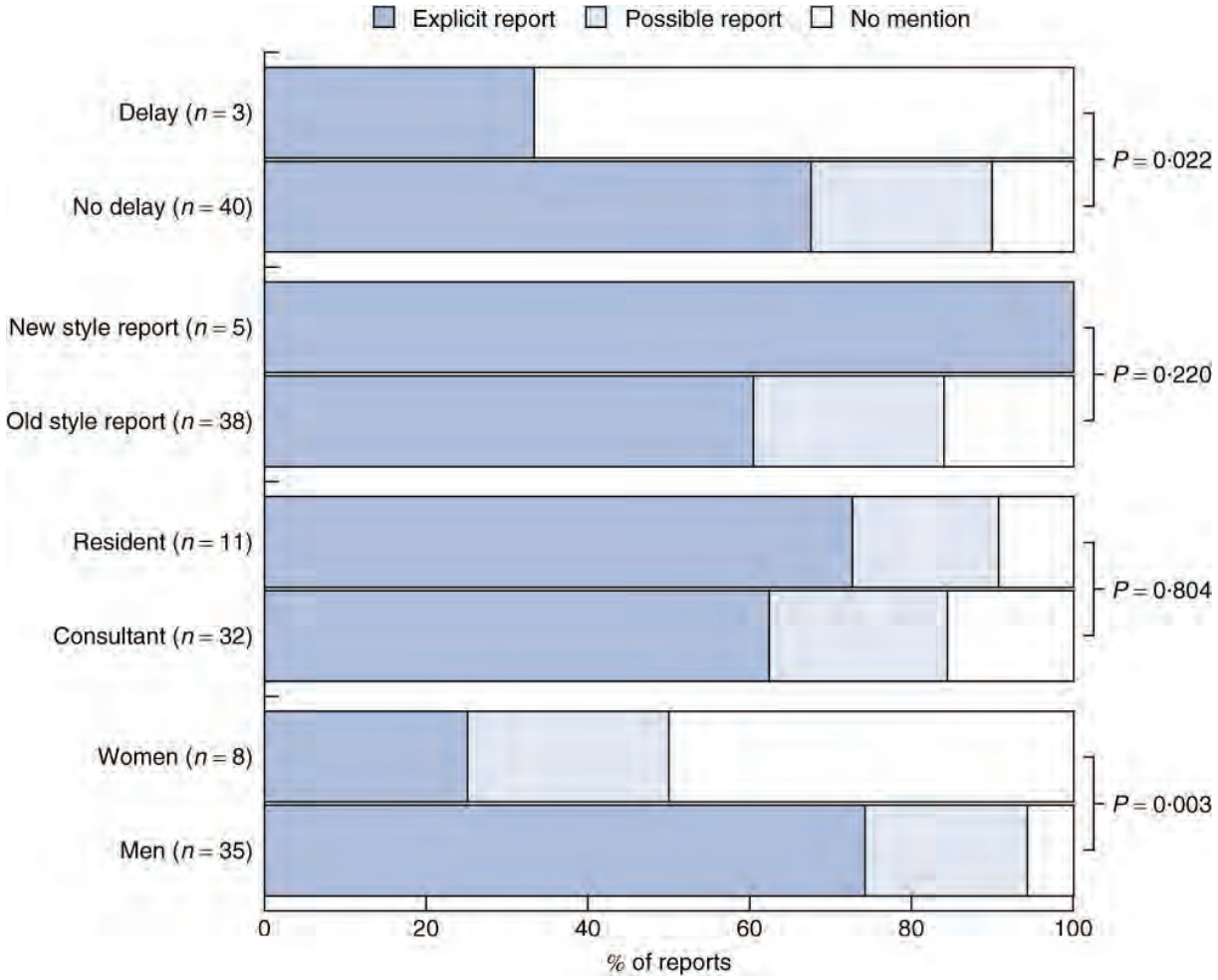

Figure 1 Impact of surgeon characteristics on the correct reporting of 43 inadvertent enterotomies. Comparisons were made with the $\chi 2$ test

Discussion

Comparison of the data from operative notes with the findings of a prospective observational study allowed the accuracy of information written in operation reports to be assessed. The present study showed significant inaccuracies in operative reports. Most worrisome is the underreporting of major adverse operative events such as an enterotomy and other iatrogenic organ injuries, with potential risk of misinterpreting the postoperative course, such as anastomotic leakage from an enterotomy repair.(9;11;12) Inaccurate reporting was not dependent on surgical experience. The present findings support the concern regarding the quality of operative reports raised in recent publications.(1-3)

The accuracy of operative reports on the presence of adhesions was poor, with a sensitivity and specificity of 85.1 and 72.4 per cent respectively. Accuracy on the performance of adhesiolysis was comparable, with a sensitivity and specificity of 74.9 and 87.5 per cent respectively. As many as one in seven enterotomies and one in three other organ injuries were not reported. Delayed dictating of operative reports was associated with more missed enterotomies. Female residents were more likely to underreport that adhesiolysis had been performed. However, these results should be interpreted carefully as only a small proportion of reports were written by a minority of women, so that individual results could have a relatively large impact on the results. Residents from training hospital B also underreported the performance of adhesiolysis significantly more often; the difference could not be attributed to an interaction with resident sex or delay in dictating.

One in seven enterotomies was missed and one in five was not reported explicitly. This corresponds with the finding that only 20 per cent of gallbladder perforations with bile spillage during laparoscopic cholecystectomy were reported.(5) It might be argued that failing to report a gallbladder perforation is less serious because the course following laparoscopic cholecystectomy is usually uneventful and does not create postoperative diagnostic dilemmas, in contrast to major abdominal procedures complicated by an inadvertent enterotomy. Unnoted operative events can delay the diagnosis of postoperative complications.(13;14) In the present cohort, eight of the 15 patients with no explicit mention of an enterotomy suffered from major complications related to surgery, such as pneumonia, intra-abdominal abscess and prolonged postoperative ileus. Diagnosis of abscess, in particular, might have been delayed in the present series, but a relationship with unnoted enterotomies was difficult to confirm.

An important question is how to improve the accuracy and completeness of operative reports. Delayed dictating of operative reports was a risk factor for unnoted enterotomies. The Dutch College of Surgeons recommends that operative reports be composed and made available within one working day.(15) Immediate dictation after the operation has become a quality indicator in the authors' department, and at present delay in writing an operative report is rare. The authors prefer immediate dictation after finishing an operation, as there is some evidence that dictating multiple reports at the end of the day might reduce accuracy.(5;7;16)

Standard or computer-generated operative reports seem to improve reporting[8,17]. A major drawback of standard operative reports is that they can lead to loss of comprehensiveness and that they apply only to commonly performed operations. During the study period a new standard operative report was introduced that focused on describing intraoperative findings. Although numbers were too small for statistical comparison, no enterotomies and only a few minor organ injuries were missing in the new reports. The sensitivity and specificity for

describing the occurrence of adhesions and adhesiolysis did not improve with the new report template. As an increasing number of procedures are performed laparoscopically, the role of videotaping might become more important. Videotaping showed more of the procedural steps with greater accuracy than written reports in a previous study.(5) A drawback of videotaping is that viewing the videos can be time consuming.

Another study demonstrated that formal teaching of dictating can also improve the reliability of operative reports.(18) The differences found in the accuracy of reporting between residents from different teaching hospitals may be due to lack of interest or formal teaching in some hospitals. A recent review of the operative notes made by Harvey Cushing revealed that his openness towards reporting of surgical mishaps helped to improve the quality of care[4]. Increasing the awareness of the negative impact of adhesions on the operative course might also diminish the proportion of unnoted adhesions, adhesiolysis and inadvertent organ injury. The awareness remains rather low in various countries, and among gynaecologists and surgeons.(19;20) The present authors reported recently on the substantial morbidity and mortality associated with adhesiolysis and inadvertent enterotomies in elective abdominal surgery; they recommended that patients be properly informed regarding adhesion-related complications during consent for an operative procedure, with the expectation that this will also increase awareness of these complications among physicians.(10)

The present study analysed only the accuracy of reports on operative findings related to adhesions. The accuracy of other important aspects of reporting might also be at stake. In a recent Dutch study, postoperative instructions were missing in 78 per cent of reports.(6) In some billing systems, inaccuracy of the operative report can also result in income deprivation.(7)

The study has shown major deficits in the reporting of adhesion-related findings. Clear and concise reporting is crucial for improved postoperative care, in medicolegal cases, and for use in medical research. Efforts need to be made to teach timely, meaningful, structured and accurate reporting of surgical procedures.

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Part II: Difficulties of adhesions during reoperations

Chapter 5: Adhesiolysis-Related Morbidity in Abdominal Surgery

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Published in: Annals of surgery; 2013; 98-106

Abstract

Objective

To determine the incidence of bowel injury in operations requiring adhesiolysis and to assess the impact of adhesiolysis on the incidence of surgical complications, postoperative morbidity, and costs.

Background

Morbidity of adhesiolysis during abdominal surgery seems an important health care problem, but the direct impact of adhesiolysis on inadvertent organ damage, morbidity, and costs is unknown.

Methods

In a prospective cohort study, detailed data on adhesiolysis were gathered by direct observation during elective abdominal surgery. Comparison was made between surgical procedures with and without adhesiolysis on the incidence of inadvertent bowel defects. Secondary outcomes were the effect of adhesiolysis and bowel injury on surgical complications, other morbidity, and costs.

Results

A total of 755 (out of 844) surgeries in 715 patients were included. Adhesiolysis was required in 475 (62.9%) of operations. Median adhesiolysis time was 20 minutes (range: 1–177). Fifty patients (10.5%) undergoing adhesiolysis inadvertently incurred bowel defect, compared with 0 (0%) without adhesiolysis ($P < 0.001$). In univariate and multivariate analyses, adhesiolysis was associated with an increase of sepsis incidence [odds ratio (OR): 5.12; 95% confidence interval (CI): 1.06–24.71], intra-abdominal complications (OR: 3.46; 95% CI: 1.49–8.05) and wound infection (OR: 2.45; 95% CI: 1.01–5.94), longer hospital stay (2.06 ± 1.06 days), and higher hospital costs [$18,579 (15,204–21,954) vs $14,063 (12,471–15,655)]. Mortality after adhesiolysis complicated by a bowel defect was 4 out of 50 (8%), compared with 7 out of 425 (1.6%) after uncomplicated adhesiolysis (OR: 5.19; 95% CI: 1.47–18.41).

Conclusions

Adhesiolysis and inadvertent bowel injury have a large negative effect on the convalescence after abdominal surgery. The awareness of adhesion-related morbidity during reoperation and the prevention of postsurgical adhesion deserve priority in research and clinical practice.

Introduction

Peritoneal adhesions develop after more than 90% of operations in the abdominal cavity, procedures frequently performed by general, vascular, and gynaecological surgeons and urologists.(1–3)

Intestinal obstruction, female infertility, and abdominal pain are well-known adhesion-related complications that negatively impact millions of lives worldwide.(1;2;4–7) Surprisingly, adhesion-related complications receive little attention in clinical practice.(8–11)

Complications that occur after adhesiolysis during repeat surgery might even form a larger burden of morbidity.8 In a retrospective cohort, the risk of inadvertent bowel defects was as high as 19%.(12) The risk of needing repeat abdominal surgery is relatively high and is expected to increase in the western world with the increase of life expectancy and developments in surgical technology.(13–17)

Little is known of the impact of adhesiolysis and related organ injury on morbidity and socioeconomic costs in comparison with other adhesion-related complications. Knowledge of the morbidity related to adhesiolysis is needed to properly inform patients before surgery to take adhesiolysis risks into account in the operative decision-making, and to improve diagnosis of postoperative complications. In addition, proper data on adhesiolysis time and the socioeconomic burden of adhesions are helpful for operative room management and health care insurance.

In this prospective study, we did a detailed assessment and analysis of adhesiolysis, (post)operative complications, and socioeconomic factors in a large cohort of elective abdominal operations (clinicaltrials.gov registration number: NCT01236625).

Methods

Study Design and Patients

This was a prospective observational study as part of the LAPAD (LAParotomy or LAParoscopy and ADhesiolysis) study. The LAPAD study was designed to assess the incidence and impact of adhesiolysis on preoperative and postoperative complications, quality of life, and socioeconomic costs. All adult patients planned for elective abdominal surgery at the Department of Surgery of the Radboud University Nijmegen Medical Center between June 2008 and June 2010 were screened for inclusion. Patients planned for admission to the surgical day-care unit were excluded because the short hospital stay did not allow for adequate follow-up.

Inclusion criterion was an elective laparotomy or laparoscopy. Exclusion criteria were age under 18 years and mental disorder. Patients were included after giving oral and written informed consent.

Relevant patient, surgical, and medical data were prospectively assessed before, during, and after hospital stay and at the outpatient clinic until 6 months after discharge. At surgery, detailed information of adhesions, adhesiolysis, and inadvertent organ damage was collected through direct observation by a trained researcher (R.B., C.S., or Y.I.) who did not take part in the operation. Evaluation of adhesions was comprised of a description of the location, for example, ventral abdominal wall, operative area, and other parts of the abdomen, grading of adhesions at these 3 locations according to the Zühlke classification, and timing the duration of adhesiolysis by stopwatch.(18) Findings were recorded into the real-time database by the

researcher present in the operating theatre. Operative and treatment decisions were made according to department guidelines or at the discretion of the surgical staff. As a rule in our institution, adhesiolysis was done by sharp dissection and not by electrocautery or ultrasonic dissection. The study was approved by the local medical ethical committee and conducted according to the revised version of the Declaration of Helsinki (October 2008, Seoul).

Variables

Primary outcomes were the incidence of adhesions, adhesiolysis time, the incidence of bowel defects, seromuscular injury, injuries to other organs and structures, and the incidence of major surgery-related complications.

A detailed description of any adhesion present was obtained by direct observation. Adhesiolysis time was measured in minutes from the start of adhesiolysis until the operative area was cleared of adhesions.

Bowel defects were classified as inadvertent enterotomy or delayed diagnosed perforation. Inadvertent enterotomy was defined as any iatrogenic, unintended full thickness bowel defect detected during operation. Preexisting fistulas or defects created while dissecting the bowel loop that harboured the fistula were not scored as inadvertent enterotomy. Delayed diagnosed perforation was defined as a bowel defect with spill of gastrointestinal content that was diagnosed postoperatively by imaging, at reoperation, or at autopsy, and that could not be explained by anastomotic leakage, bowel ischemia, or any other obvious causes of leakage unrelated to adhesiolysis.

Seromuscular injury was defined as injury to the serosal and muscular layers of the bowel, without visualization of the bowel lumen or spillage of bowel content. Other intraoperative injuries were comprised of any injury to the spleen, liver, pancreas, urogenital structures, lung, vascular structures, or nerves.

Postoperative complications noted as major surgery-related complications were death, wound infection (categorized as superficial or deep), anastomotic leak, fistula and abscess, pneumonia, sepsis, haemorrhage, and urinary tract infection. Major surgery-related complications were defined according to the criteria of the International Classification of Diseases, Tenth Revision, the National Nosocomial Infections Surveillance System, the Centre for Disease Control and Prevention, or according to the decision of the senior medical staff of the department.

Secondary outcomes were other morbidity and socioeconomic costs including total operative time, blood loss, recovery unit stay, hospital stay, unplanned or prolonged intensive care unit admission, intensive care unit stay, parental feeding, tube feeding, incidence of emergency reoperations, and incidence of readmission to the hospital within 30 days after discharge.

Cost analysis was performed in United States dollars (unit of analysis) and included only the direct hospital costs: operation costs, ward stay, intensive care unit stay, extra charges for parental and tube feeding, postoperative diagnostics, reoperation costs, and blood products. Cost calculations were performed using the guidelines for cost analysis of the Dutch College of Health Insurance Companies using a top-down approach.(19) Operation costs were calculated based on total anaesthesia time using operating room costs of $1390 per hour, including personnel, material, and overhead costs. Total costs for the surgical ward and intensive care unit were $661 and $2289 per day, respectively, and included basic nutritional

costs. More than basic parental and tube feedings were considered as extra nutritional costs. Diagnostic and reoperation costs were calculated using the 2004 price lists for medical procedures by the Dutch College of Health Insurance Companies. Medication costs and blood products costs were calculated according to the standardized price list of the Dutch College of Health Insurance Companies updated for June 2008.(20)

Baseline demographics included sex, age, body mass index, Alcohol Use Disorders Identification Test alcohol abuse index,(21) history of abdominal operations, number of laparotomies in history, number of laparoscopies in history, history of generalized peritonitis, American Society of Anaesthesiologists classification, P-Possum score, Revised Cardiac Risk Index, diabetes mellitus, extent of surgery, surgical approach (open or laparoscopic), anatomical site of operation [upper gastro-intestinal, lower gastro-intestinal, hepatobiliary–pancreatic, abdominal wall, or other], and level of surgical experience (surgeon or resident).

Statistical Methods

Univariate comparisons were performed using linear regression for continuous and logistic regression for dichotomous data. Effect size was expressed as mean difference with standard deviation for continuous data and odds ratios (ORs) for dichotomous data. Despite the large number of patients, differences in baseline factors between the groups were expected because adhesions are mostly due to prior surgery. To avoid potential bias by an unequal distribution of risk factors, we calculated an adjusted effect size using multivariate linear and logistic regression for continuous and dichotomous data, respectively. All factors with unequal distribution at baseline with $P < 0.010$ were included in the multivariate model, except a history of peritoneal surgery and generalized peritonitis, and peritoneal surgery and previous peritonitis were considered pathogenic for adhesion formation and were not expected to have further independent adverse effects on treatment outcomes. In composite outcomes, statistical results were presented for both the composite outcome and the individual components of the composite. Costs are presented as mean cost with a 95% confidence interval (CI). Statistical comparison of costs was performed by multivariate regression on the logistically transformed values of the costs to reduce the impact of outliers. All outcomes were assessed per operation and analysed according to an intention-to-treat, unless otherwise stated.

In the subgroup of operations with adhesiolysis, we compared major surgery-related complications, other morbidities, and costs between adhesiolysis complicated by bowel defects and uncomplicated adhesiolysis.

In an additional analysis, we calculated the risk for enterotomy, seromuscular injury, and other organ injury by categorizing adhesiolysis time (none, 1–15, 16–30, 31–60, and >60 min).

There was only minimal missing data; thus, we excluded per analysis those cases with missing data. We used SPSS for Windows version 16.0 software (SPSS, Chicago, IL) for statistical analysis. Values of $P < 0.05$ were considered significant.

Results

Cohort and Baseline Comparison

A total of 844 consecutive elective surgeries were screened for eligibility; 89 operations were excluded. Main reasons for exclusion were cancellation of the operation (N = 38), refusal to participate (n = 11), and mental incompetence of the patient (N = 8). A total of 755

operations carried out in 715 patients were included in the study (Fig. 1). Adhesiolysis time was missing in 4 operations (0.5%). There were no further missing data.

The incidences of adhesions and adhesiolysis were 497 out of 755 (65.8%) and 475 out of 755 (62.9%), respectively. Most common etiologies for the presence of adhesions were previous intra-abdominal surgery and peritonitis (Table 1); mean adhesiolysis time was 20 minutes (range: 1–177). Adhesions to the incision scar of a previous operation were found in 399 (80.3%) of operations with adhesions, whereas in 416 operations (83.7%), adhesions were present in the operative area and in 329 operations (63.6%), adhesions were found in other parts of the abdomen. Median Zühlke score was 2 (range: 1–5) at all 3 locations. Severe adhesions (Zühlke score: 3 or 4) were found under a previous scar in 233 operations (46.9%) with adhesions, at the operative area in 235 operations (47.3%), and in other parts of the abdomen in 160 operations (32.2%). Patients who had adhesions and no prior surgery or general peritonitis in their history usually only had a few low-grade adhesions with a median adhesiolysis time of 5 minutes (range: 1–93). Those adhesions were mostly located adjacent to a local inflammatory process or tumour.

Table 1 shows the baseline data for the 2 groups. There were significant differences in the anatomical location of the operation ($P < 0.001$), operative severity ($P < 0.001$), surgical approach ($P = 0.01$), and body mass index ($P = 0.003$).

Impact of Adhesiolysis on Peroperative Complications

The incidence of full thickness bowel defects was 10.5% in the adhesiolysis group and 0% in the nonadhesiolysis group ($P < 0.001$). During 43 operations, there was a median of 1 (range: 1–9) inadvertent enterotomy. Bowel resection and anastomosis were required in 24 operations (55.8%) with 1 or more enterotomies, and in the remaining operations, enterotomies were repaired by primary suturing. Injury to the seromuscular layer occurred in 131 procedures (27.6%) with adhesiolysis compared with 11 (3.9%) without adhesiolysis ($P < 0.001$). As a rule, seromuscular injuries were repaired by suturing.

Delayed diagnosed perforation occurred after 10 surgeries. A delayed diagnosed perforation occurred after 8 out of 142 seromuscular injuries (5.6%) and 3 out of 43 enterotomies (7.0%). The 3 patients with a delayed diagnosed perforation after an enterotomy also had seromuscular injuries. In 2 patients with delayed diagnosed perforation (20.0%), no seromuscular injury or enterotomy occurred during initial operation

Injury to other organs was 8.6% in the adhesiolysis group compared with 2.5% in the nonadhesiolysis group ($P = 0.001$). Most common injuries in the adhesiolysis group were to the liver ($n = 14$), vascular structures ($n = 11$), urogenital structures ($n = 8$), spleen ($n = 4$), and bile ducts ($n = 3$). Injuries in the nonadhesiolysis group were comprised of vascular structures ($n = 4$), spleen ($n = 2$), and bile duct ($n = 1$).

After adjustment for anatomical location, operative severity, surgical approach, and body mass index, the difference in incidence of seromuscular injury and other organ injuries remained significant (Fig. 2A). Multivariate analysis could not be conducted for bowel defects as none occurred in the nonadhesiolysis group.

The 43 inadvertent enterotomies occurred exclusively in patients who underwent open surgery. One patient (2.9%) who underwent laparoscopy had a delayed diagnosed perforation compared with 9 (2.0%) who underwent open surgery ($P = 0.75$).

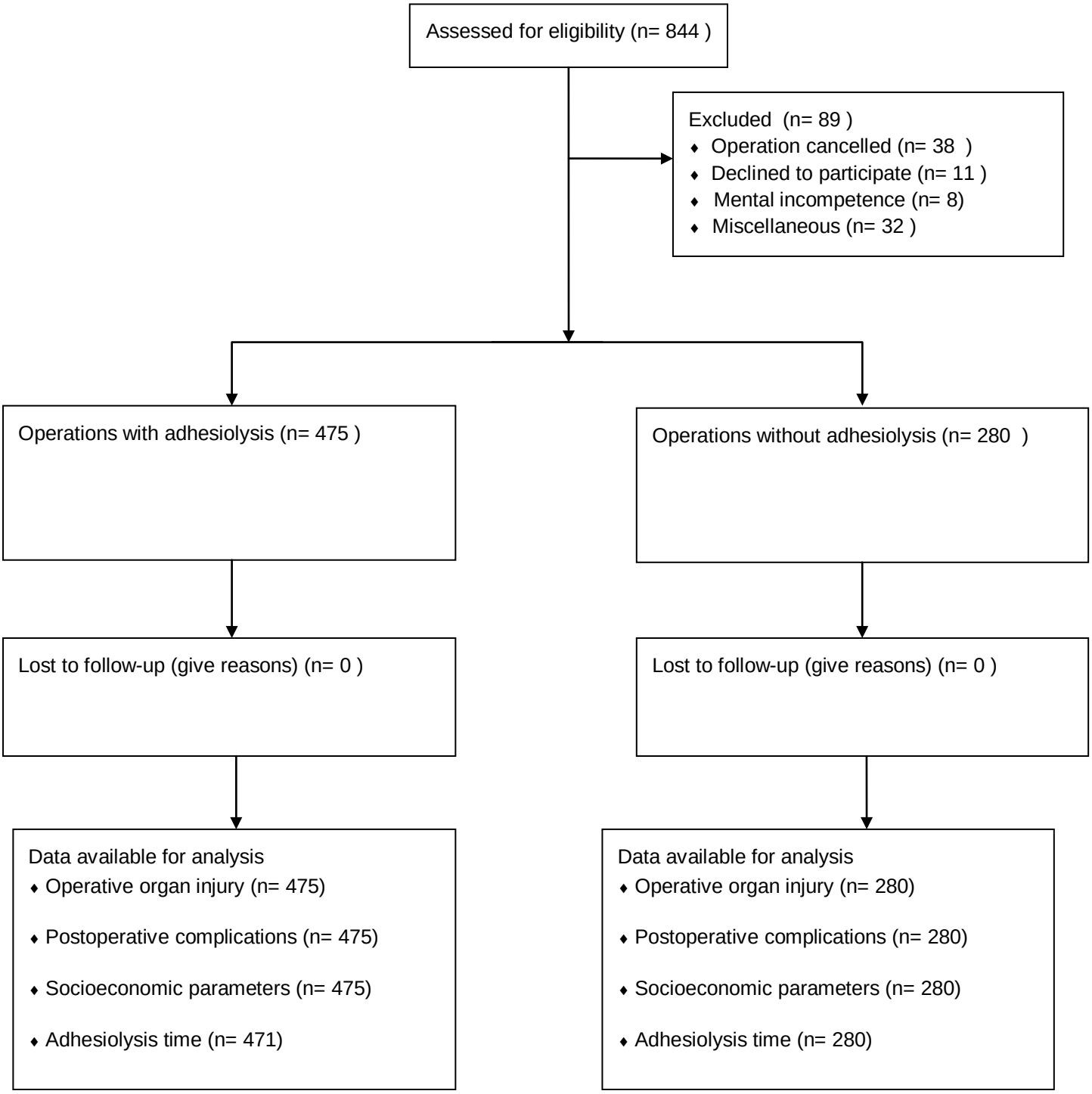


Figure 1. Flow diagram of the included operations.

Table 1 Baseline Comparison Between Operations With and Without Adhesiolysis

	Adhesiolysis group (n=475)	**No adhesiolysis group (n=280)**	**P- value**
Demographics			
Sex			
Male	264 (55.6%)	116 (59.3%)	
Female	211 (44.4%)	114 (40.7%)	.32
Age*	58.1 ± 13.8	59.4 ± 14.1	.23
BMI*	26.0 ± 4.8	25.1 ± 3.8	.003
Smoking status			
Non Smoker	163 (34.3%)	104 (37.3%)	
Ex- Smoker	210 (44.2%)	130 (46.6%)	.20
Smoker	102 (21.5%)	45 (16.1%)	
Alcohol abuse			
Low Risk	450 (94.9%)	261 (93.5%)	
Moderate Risk	18 (3.8%)	12 (4.3%)	.60
High Risk	6 (1.3%)	6 (2.2%)	
Peritoneal Surgery in History			
Yes	412 (86.7%)	90 (32.1%)	
No	63 (13.3%)	190 (67.9%)	<.001
Laparotomies in History†	2 (0-56)	0 (0-3)	<.001
Laparoscopies in History†	0 (0-2)	0 (0-1)	<.001
Generalized Peritonitis in History			
Yes	66 (13.9%)	1 (0.4%)	
No	409 (86.1%)	279 (99.6%)	<.001
Preoperative risk assessement			
ASA Slassification			
I	77 (16.2%)	46 (16.4%)	
II	284 (59.8%)	172 (61.4%)	
III	113 (23.8%)	62 (22.1%)	.83
IV	1 (0.2%)	0 (0.0%)	
P- Possum Score*	6.2 ± 9.8	6.0 ± 8.7	.79
Revised Cardiac Risk Index			
2	396 (83.4%)	222 (79.3%)	
3	66 (13.9%)	45 (16.1%)	.25
4	13 (2.7%)	13 (4.6%)	
Diabetes Mellitus in History			
Yes	43 (9.1%)	29 (10.4%)	
No	432 (90.9%)	251 (89.6%)	.56
Operative Severity			
Minor	0 (0.0%)	2 (0.7%)	
Moderate	22 (4.6%)	14 (5.0%)	
Large	311 (65.5%)	134 (47.9%)	<.001
Major	142 (29.9%)	130 (46.4%)	
Characteristics of planned operation			
Open surgery/Laparoscopy			
Open surgery	440 (92.6%)	244 (87.1%)	
Laparoscopy	35 (7.4%)	36 (12.9%)	.01
Anatomical site of primary intervention			
Upper GI- tract	25 (5.3%)	58 (20.7%)	
Lower GI- tract	219 (46.1%)	122 (43.6%)	
HPB	82 (17.3%)	61 (21.8%)	
Abdominal wall	115 (24.2%)	9 (3.2%)	<.001
Other	34 (7.2%)	30 (10.7%)	
Surgical Experience			
Surgeon	330 (69.5%)	194 (69.3%)	
Resident	145 (30.5%)	86 (30.7%)	.96

*= mean ± standard deviation ; †= medain (range)

The incidence of enterotomy was 0.0% in virgin abdomens, 2.5% after 1, 8.7% after 2, and 15.5% after 3 or more prior abdominal operations. A high Zühlke score correlated with an increased incidence of enterotomy. Incidence of enterotomy was 0% in grade 1, 0.7% in grade 2, 8.9% in grade 3, and 36.4% in operations with grade 4 adhesions in the operative area. Enterotomies were found in 2 operations (0.6%) without adhesions to a previous scar, 0% with grade 1, 2.2% with grade 2, 12.0% with grade 3, and 26.9% with grade 4 adhesions to a previous scar. The correlation between adhesion grade and enterotomies was less strong for adhesions in other parts of the abdomen with an incidence of 0.5% without adhesions, 2.9% with grade 1, 7.4% with grade 2, 19.5% with grade 3, and 18.9% with grade 4 adhesions. The incidence of enterotomy, seromuscular injury, and other organ injury significantly increased with longer adhesiolysis time (Figs. 2A–C).

DISCUSSION

In this study, adhesiolysis-induced morbidity was high: a median of 20 minutes increase of operative time, a 1 in 10 risk of inadvertent bowel defects, a sevenfold increase in seromuscular injury, and a threefold to fourfold increase in other organ injury. Adhesiolysis, particularly with the resulting bowel defects, led to more postoperative sepsis, intra-abdominal complications including surgical site infections, a longer hospital stay, more readmissions, and increased costs.

Adhesiolysis at repeat surgery has received less attention than bowel obstruction and infertility in reports assessing the clinical and socioeconomical burden of postoperative adhesions. Underestimation of the related morbidity and the passiveness of many physicians, who consider adhesiolysis an annoying but unavoidable part of redo surgery, account for the paucity of reports on the consequences of adhesiolysis. The available literature is limited to small series in specific surgical areas or retrospective series in which previous surgeries or rehospitalisation are taken as the measure of adhesiolysis.(2;12;22;23) We designed a large prospective study to provide accurate incidences of adhesiolysis-related morbidity and socioeconomical costs. This study provided for continuous observation of the surgical procedures in the operating theatre by a trained researcher who did not take part in the surgery. This enabled the collection of reliable data that most probably could not have been retrieved from other sources such as operative reports.(24–26)

The long total adhesiolysis time reflected the high complexity of these operations: when the adhesiolysis was longer than 1 hour, 40% of the operations resulted in bowel defects. Previous studies have used adhesion scores and entry times as the parameter for complexity.(18;23) However, an adhesion score is subjective and loses merit when adhesions are present in different parts of the abdominal cavity. Entry time is only a useful parameter when opening a previous abdominal incision and reflects a minor part of total adhesiolysis time and adhesiolysis-related complications.(12;23) We also had difficulty in distinguishing between adhesiolysis required just to enter the abdomen and adhesiolysis required to free the operative area in cases with massive adhesion formation to the ventral and lateral abdominal walls.

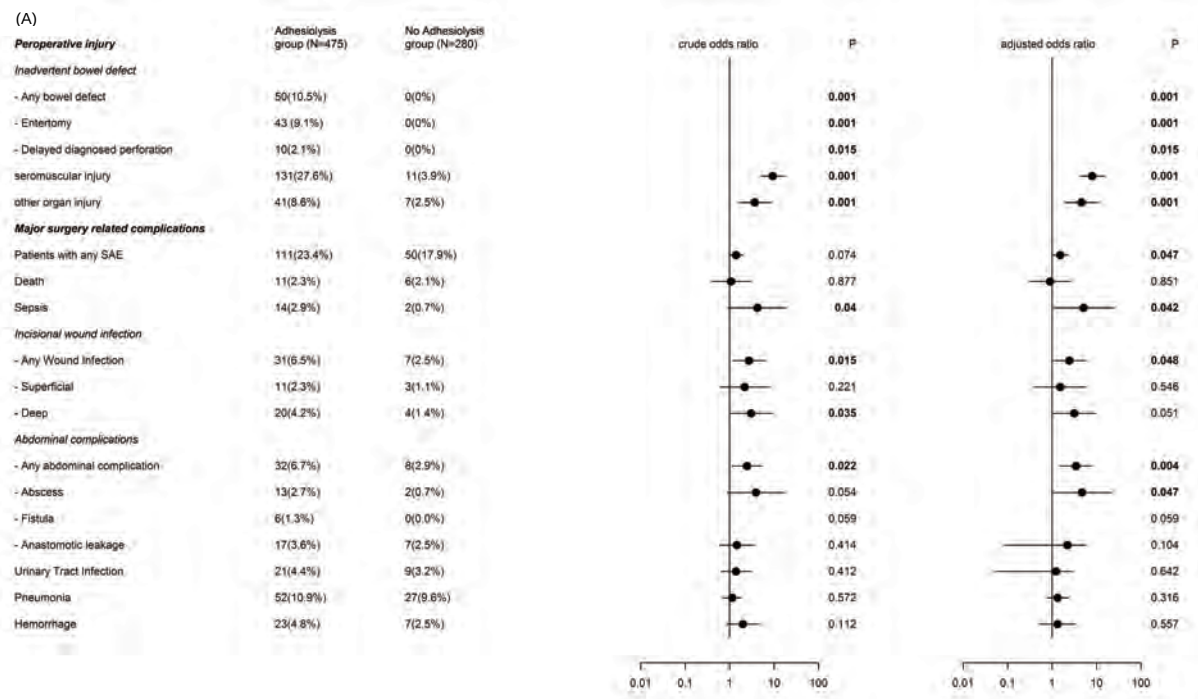
Table 2 Morbidity Outcomes Compared Between Operations With and Without Adhesiolysis and Compared Between Surgery With or Without Inadvertent Bowel Defect in the Subgroup of Operations With Adhesiolysis

	Adhesiolysis group (n=475)	**No adhesiolysis group (n=280)**	**Crude OR (95% CI)**	**P-value**	**Adjusted OR (95% CI)**	**P Value**		**Enterotomy/ DDP (n=50)**	**No enterotomy/ DDP (N=425)**	**OR (95% CI)**	**P-value**
Operation time (min.)	195 ± 98*	179 ± 89*	**16.2 ± 7.1**†	**.020**	**22.5 ± 6.0**†	**<.001**		221 ± 101*	192 ± 97*	29.5 ± 14.56†	.05
Blood loss (ml)	934 ± 1 630*	725 ± 905*	**209 ± 106**†	**.024**	**305 ± 101**†	**.003**		1 119 ± 1 438*	912 ± 1 652*	207 ± 244†	.35
Recovery unit stay (hours)	7.9 ± 10.9*	6.4 ± 9.0*	**1.49 ± 0.77**†	**.043**	**2.21 ± 0.74**†	**.003**		7.2 ± 8.8*	8.0 ± 11.2*	-0.8 ± 1.6†	.54
Hospital stay (days)	11.5 ± 16.5*	9.4 ± 8.5*	**2.06 ± 1.06**†	**.024**	**3.14 ± 1.08**†	**.004**		20.6 ± 33.1*	10.4 ± 12.8*	**10.2 ± 2.4**†	**.04**
Unplanned/ prolonged ICU admission	77 (16.2%)	51 (18.2%)	0.87 (0.59- 1.28)	.478	1.09 (0.70- 1.70)	.70		14 (28.0%)	63 (14.8%)	**2.24 (1.14- 4.38)**	**.02**
ICU stay (days)	1.9 ± 11.6*	1.0 ± 3.4*	0.94 ± 0.71†	.101	1.22 ± 0.73†	.10		9.3 ± 31.8*	1.08 ± 5.2*	8.25 ± 1.70†	.07
Parenteral feeding	77 (16.2%)	25 (8.9%)	**1.97 (1.22- 3.18)**	**.005**	**2.00 (1.19- 3.34)**	**<.001**		20 (40.0%)	57 (13.4%)	**4.30 (2.29- 8.09)**	**<.001**
Parental feeding (days)	3.0 ± 11.2*	1.4 ± 5.9*	**1.58 ± 0.72**†	**.012**	**1.95 ± 0.74**†	**.009**		11.7 ± 26.2*	2.0 ± 7.2*	**9.73 ± 1.62**†	**.01**
Tube feeding	95 (20.0%)	92 (32.9%)	**0.511 (0.37 – 0.72)**	**<.001**	**0.99 (0.65- 1.49)**	>.999		10 (20.0%)	85 (20.0%)	1.00 (0.48- 2.08)	>.999
Unplanned tube feeding	67 (14.5%)	44 (15.7%)	0.88 (0.58 – 1.33)	.546	1.09 (0.70- 1.70)	.21		10 (20.0%)	57 (13.4%)	1.61 (0.77- 3.41)	.21
Tube feeding (days)	3.3 ± 11.8*	3.55 ± 6.3*	-0.24 ± 0.76†	.718	0.47 ± 0.76†	.54		6.14 ± 23.7*	3.0 ± 9.5*	3.17 ± 1.76†	.35
Reoperations											
Any	74 (15.6%)	28 (10.0%)	**1.66 (1.05**	**.030**	1.62 (0.98	.06		16 (32.0%)	58 (13.6%)	**2.98 (1.55**	**.001**
Relaparotomy	57 (12.0%)	19 (6.8%)	**1.87 (1.09**	**.021**	1.68 (0.94	.08		13 (26.0%)	44 (10.4%)	**3.04 (1.50**	**.001**
Central Venous Line	11 (2.3%)	7 (2.5%)	0.93 (0.35	.873	1.13 (0.41	.81		1 (2.0%)	10 (2.4%)	0.85 (0.11	.88
Other	16 (3.4%)	6 (2.1%)	1.59 (0.62	.333	**2.03 (0.67- 6.15)**	.21		5 (10.0%)	11 (2.6%)	**4.18 (1.39 – 12.58)**	**.006**
Readmissions within 30 days of discharge	69 (14.5%)	20 (7.1%)	**2.21 (1.31- 3.72)**	**.002**	**2.37 (1.36- 4.13)**	**.002**		13 (26.0%)	56 (13.2%)	**2.32 (1.16- 4.62)**	**.02**

*= mean ± SD ; †= Unadjusted coefficient ± SD;

FIGURE 2. A, Crude and adjusted ORs with 95% CI for (post)operative complications compared between surgery with and without adhesiolysis. B, ORs with 95% CI of postoperative complications after surgery with adhesiolysis compared between surgery with or without inadvertent bowel defect.

(A)



(B)

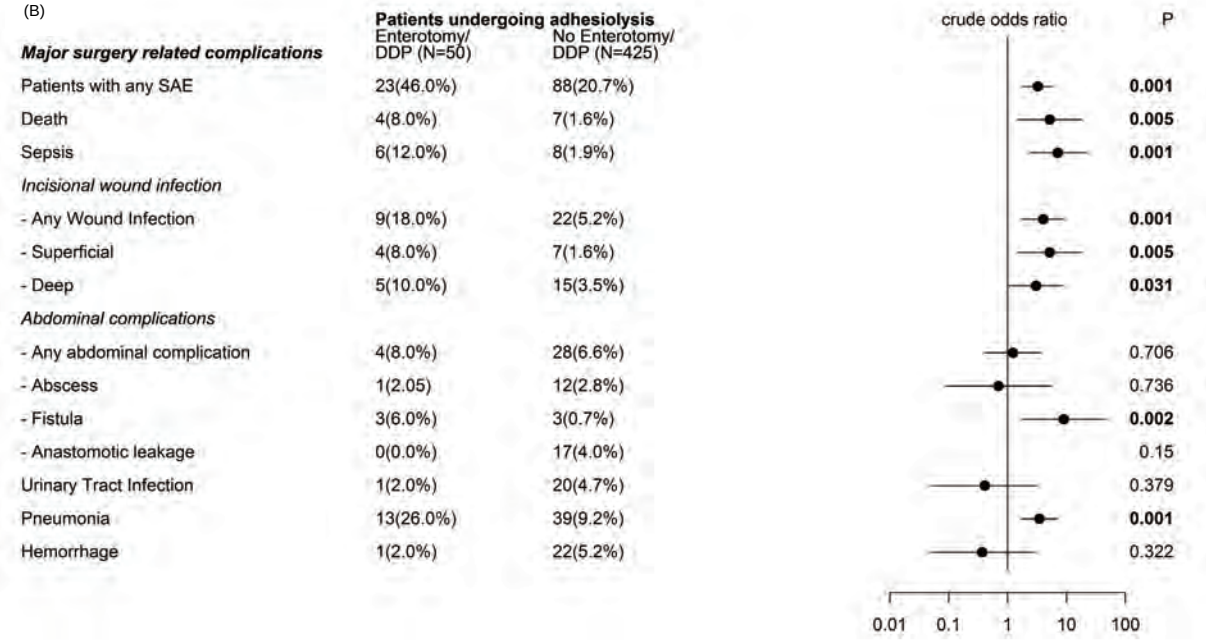
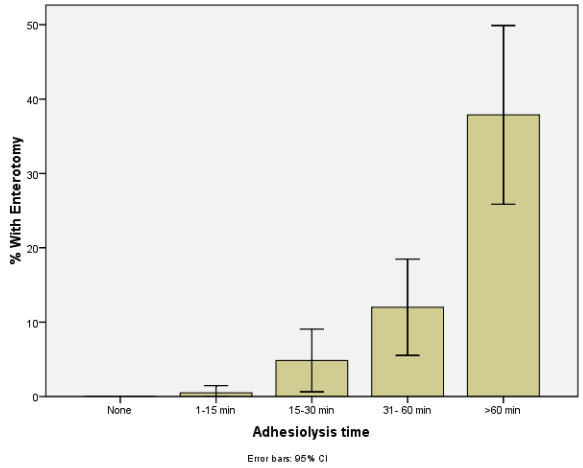


FIGURE 3. Risk of inadvertent organ injury with 95% CI stratified by adhesiolysis time: A, Enterotomy. B, Seromuscular injury. C, Other organ injury.

A



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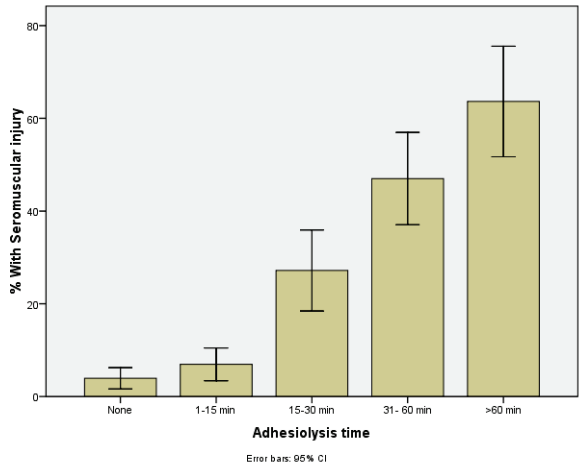

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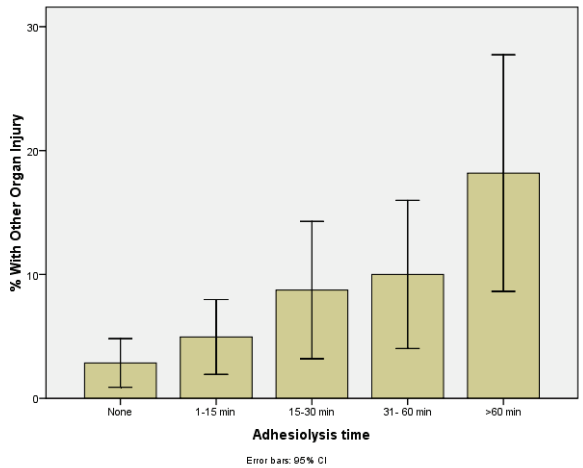

Table 3 Socioeconomical Cost Analysis Compared Between Operations With and Without Adhesiolysis and Compared Between Surgery With or Without Inadvertent Bowel Defect in the Subgroup of Operations With Adhesiolysis

	Adhesiolysis group (n=475) mean(95% CI)	**No adhesiolysis group (n=280) mean(95% CI)**	**P**	**Enterotomy/ DDP (n=50) mean(95% CI)**	**No Enterotomy/ DDP (N=425)) mean(95% CI)**	**P**
Operation cost	5204 (4986 – 5421)	4871 (4611 – 5131)	**<.001**	5 840 (5 143 – 6536)	5 129 (4 900 – 5358)	**.03**
Ward stay	6090 (5556 – 6624)	5438 (4894 – 5982)	.12	7 261 (5 719 – 8 804)	5 952 (5 383 – 6 522)	**.04**
ICU stay	4551 (2092 – 7009)	2349 (1405 – 3293)	.11	21 828 (648 – 43 007)	2 518 (1 350 – 3 686)	**.006**
Extra charges for parenteral/ tube feeding	945 (653 – 1237)	529 (331 – 727)	.93	3 411 (1 290 – 5532)	654 (453 – 856)	**<.001**
Medication	901 (451 – 1352)	382 (303 – 462)	**.01**	3 217 (0 – 7 196)	629 (427 – 832)	**<.001**
Diagnostics (radiology, pathology and microbiology)	475 (368 – 581)	400 (324 – 476)	.51	1 098 (350 – 1 846)	401 (321 – 481)	.13
Reoperations	177 (128 – 225)	94 (51 – 136)	**.01**	434 (181 – 746)	143 (100 – 186)	**<.001**
Blood products	274 (171 – 376)	99 (56 – 141)	**<.001**	811 (0 – 1 637)	211 (148 – 273)	**.04**
Total costs	18 579 (15 204 – 21 954)	14 063 (12 471 – 15655)	**<.001**	43 784 (16 629 – 70 938)	15 614 (13 642 – 17 586)	**<.001**

The incidence of inadvertent enterotomy in this study was lower than the 19% previously reported by our group.(12) The increased awareness of the impact of adhesiolysis and the modification in our department's protocol for cutting adhesions may have contributed to the decrease in bowel defects. Another explanation could be the strict definition of iatrogenic bowel defects, which no longer included enterotomies in the proximity of a pre-existing bowel fistula. The presence of an observer might also have raised the surgeon's vigilance to avoid injury. We noted, however, that the operating teams rapidly became accustomed to having an observer in the operating theatre.

The need for adhesiolysis in 60% of the surgical procedures and the low number of laparoscopies could limit the generalizability of the study results. However, these percentages have been consistent in our academic department during the past decade, and they compare with those in a large multicentre series of patients who underwent elective colorectal surgery for a benign disease.(27;28) The percentage also results from the exclusion of short-stay surgery, which is predominantly minimally invasive surgery in virgin abdomens and emergency abdominal surgeries.

Our article is the first showing adhesiolysis as a risk factor for postoperative surgical complications, longer hospital stays, more readmissions, and increased costs. Inadvertent bowel defects increased even more morbidity and costs and they also caused significant mortality, which agrees with the results from our retrospectively collected data.(12;22) Incisional wound infection was the most prominent complication reflecting the longer adhesiolysis-related operating times and increased blood loss, events that are used to estimate the risk of surgical site infection.(29) The high morbidity, long hospital stay, and high costs of a surgical site infection are well known from other reports.(30;31) The portion of patients with surgical site infection after previous surgery could not be identified from the patients' medical charts. A history of peritonitis could be reliably obtained and was not a significant risk factor for surgical site infection.

The economical burden of adhesive bowel obstruction in the United States is at least 2 billion dollars annually.(32) The cost of adhesive small bowel obstruction per patient is estimated at $9700 for operatively treated patients and at $4000 for conservatively treated patients.(33;34) The cost data from this prospective study permitted an accurate calculation of the in-hospital costs related to adhesiolysis. These costs were $4500. Taking into account that adhesiolysis was required in 60% of the patients and that only about 2% to 4% of the patients acquire an adhesive small bowel obstruction after abdominal surgery, the economical burden of adhesiolysis is likely to exceed that of adhesive small bowel obstruction.(2;35) These cost calculations can be used for reimbursement purposes and to re-evaluate decisions concerning the use of barriers to prevent adhesion formation in elective abdominal surgery. Current cost-effectiveness analyses have focused on prevention of adhesive small bowel obstruction and, in many countries, have not lead to the routine use of anti-adhesive barriers.(33) With the projected increase in more repeat abdominal surgeries because of a longer life expectancy and newer technologies, prevention of adhesiolysis-related morbidity might be even more cost-effective.

The huge burden of adhesiolysis-related morbidity in elective abdominal surgery has consequences for the daily practice of physicians with regard to counselling patients. Less than 10% of surgeons inform their patients about the risk of adhesions.(9) The high risk of

adhesiolysis complicating the immediate postoperative course warrants routine informed consent.(11) In an analysis of medicolegal claims for complications after adhesiolysis, inadvertent bowel injury accounted for a considerable portion of both submitted and granted complaints.(36;37)

This study has demonstrated the substantial clinical and socioeconomical burden of adhesiolysis, particularly when a bowel defect occurs. All physicians treating patients with disorders of the abdominal cavity that might require surgery should be aware of the adverse effects of adhesiolysis. Our data can be of help when counselling patients before surgery, when physicians and health care providers make decisions on implementing anti-adhesive strategies, and for the reimbursement policy of insurance companies.

ACKNOWLEDGEMENTS

The authors thank Patrica G. Anderson for kindly reviewing the manuscript contextually and grammatically.

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Part II: difficulties of adhesions during reoperations

Chapter 6: Enterotomy Risk in Abdominal Wall Repair: a Prospective Study

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Published in: Annals of surgery; 2012; 280-7

Abstract

Objectives

To establish the incidence and predictive factors of enterotomy made during adhesiolysis in abdominal wall repair and to assess the impact of enterotomies and long-lasting adhesiolysis on postoperative morbidity such as sepsis, wound infection, abdominal complications and pneumonia, and socioeconomic costs.

Background

Adhesions frequently complicate surgical repair of abdominal wall hernia. Enterotomies made during adhesiolysis specifically have a large impact on morbidity of patients, especially surgical site infections. Little is known on the incidence and burden of enterotomies and long-lasting adhesiolysis in abdominal wall repair.

Methods

Between June 2008 and June 2010 demographics, disease characteristics and perioperative data of all patients undergoing elective abdominal wall repair were included in a prospective cohort study that was focused on adhesiolysis-related problems. A trained researcher observed all surgeries and collected data on adhesion location, tenacity, adhesiolysis time, and inadvertent organ damage such as enterotomies. Primary outcome was the incidence of enterotomy, and predictive factors for enterotomy were assessed through univariate and multivariate analyses. In addition, we evaluated the impact of adhesiolysis and enterotomy on morbidity.

Results

A cohort of 133 abdominal wall repairs was analyzed. Adhesiolysis was required in 124 (93.2%), with a mean adhesiolysis time of 35.7 ± 29.8 minutes. Thirty-three enterotomies were made in 17 patients (12.8%). Two patients had a delayed diagnosed bowel perforation. Adhesiolysis time, hernia size greater than 10 cm, and fistula were significant predictive factors in univariate analysis. In multivariate analysis, only adhesiolysis time was a significant and independent predictive factor for enterotomy (P = 0.004). Trends toward an increased risk were seen for patients with mesh in situ and hernia size greater than 10 cm. Patients with enterotomy had significantly more urgent reoperations (P=0.029), and they more often required parenteral feeding (P=0.037).Moreover, patients with extensive adhesiolysis (adhesiolysis time, >30 minutes) more often suffered from wound infection (9/63 vs 2/70; P = 0.025), abdominal complications (5/63 vs 0/70; P = 0.022), and sepsis (4/63 vs 0/70; P = 0.048).

Conclusions

One in 8 patients undergoing abdominal wall repair suffer inadvertent enterotomy following adhesiolysis. Adhesiolysis time predicts enterotomy. Morbidity in patients with extensive adhesiolysis and adhesiolysis complicated by enterotomy is high, inducing longer hospital stay and increased health care utilization.

Introduction

Abdominal wall defect is a common indication for surgery and poses a significant health problem. Incisional ventral hernia is the most frequent abdominal wall defect and occurs in about 10% to 20% of patients undergoing open surgery.(1;2) The incidence might even by higher in obese patients and after recurrent abdominal surgeries.(1–3) Symptoms of incisional ventral hernia include pain and discomfort at the hernia site, limitations in daily activities, and intestinal obstruction. A complex incisional ventral wall hernia may present with enterocutaneous fistula–associated problems such as skin infection, wound care difficulties, and malnutrition.(4)

About one third of patients with ventral hernia undergo surgical repair by synthetic mesh, autologous tissue repair, or a combination of both.(5–7) Short-term complications of repairs are frequent and include postoperative haemorrhage, seroma formation, surgical site infection, and mesh infection.(7–11)

A largely neglected intraoperative complication of both open and laparoscopic abdominal wall repair is an inadvertent enterotomy following adhesiolysis.(12) Enterotomy increases the risk for unplanned enterectomy, wound infection, reoperations, and fistula formation and jeopardizes reconstruction with mesh. In a retrospective study of repeat laparotomy after all types of abdominal surgery, inadvertent enterotomy was correlated with a high number of complications, urgent reoperations, intensive care unit (ICU) admissions, and need for parenteral feeding.(13) The mortality rate of patients with inadvertent enterotomies varies between 8% and 50%, depending on whether the enterotomy is recognized immediately during surgery or with delay in the postoperative phase.(8)

With a reported incidence of 90% adhesions after intraperitoneal surgery, adhesiolysis is an expected part of incisional ventral hernia repair.(14;15) The close proximity of the scarred skin, peritoneum, and bowel in patients with ventral hernia poses the bowel at risk to be injured at open abdominal entry or trocar insertion for laparoscopic repair. Inadvertent enterotomy has been reported in about 2% to 7% of patients with elective hernia repair, but in case of recurrent and complicated hernia surgery, this percentage seemed even higher. (8;9;16;17)

Little is known about the clinical and socioeconomic burden of adhesiolysis and inadvertent enterotomy in ventral hernia repair. One review reported the combined incidence of enterotomies from a multitude of mostly smaller series of ventral hernia repair.(8) Two studies specifically reviewed the incidence in larger cohorts of patients on the basis of operation codes and notes of mortality and morbidity rounds.(9;18) However, bias due to self-reporting and the retrospective nature of these studies might have led to an underestimation of the problem.

Knowing the impact of adhesiolysis and the incidence and morbidity of inadvertent enterotomy is important to make decisions in abdominal wall repair and to increase the awareness of adhesions, inducing complications during peritoneal surgery. In addition, the patient consent process requires surgeons to adequately inform patients undergoing incisional ventral hernia repair of risks associated with adhesiolysis.

We aimed to prospectively assess the incidence of inadvertent enterotomy in a large group of consecutive patients undergoing abdominal wall repair and to identify possible predictive

factors. We analyzed the impact of adhesiolysis and inadvertent enterotomy on morbidity and mortality, and health care utilization.

Methods and Materials

Study Design

This was a prospective observational study as part of the LAParotomy or LAParoscopy and ADhesions (LAPAD) study (clinicaltrials.gov registration number NCT01236625). The LAPAD study was designed to assess the incidence and impact of adhesiolysis on operative and postoperative complications, quality of life, and socioeconomic costs. All adult competent patients undergoing elective laparotomy or laparoscopy admitted to the surgical ward between June 1, 2008, and June 2, 2010, at the Department of Surgery of the Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands, were eligible for participation in the LAPAD study. Surgical patients treated in daycare were not screened for eligibility because early postoperative follow-up for complications was not adequate. During the operation, detailed information of adhesions, adhesiolysis, and inadvertent organ damage was collected through direct observation by a trained researcher (R.B.) not taking part in the surgery. Relevant data related to patients and to surgical and medical procedures were prospectively assessed during hospital stay and at the outpatient clinic until 6 months after discharge. Operative and treatment decisions were taken according to department guidelines or at the discretion of the surgical staff. In all cases, both sharp dissection and electrocautery were used for adhesiolysis. As a rule, however, electrocautery was avoided in dense adhesions (Zühlke score 3 and 4) to prevent bowel injury from thermal injury and necrosis.(19,20) The study was approved by the local medical ethical committee and conducted according to the revised version of the Declaration of Helsinki (October 2008, Seoul).

Cohort Selection

For each patient participating in the LAPAD study, the planned and actual operative procedures were noted using the hospitals operation coding system. The indications for the procedure were defined following the International Statistical Classification of Diseases and Related Health Problems, version 10 (ICD-10). The current study group was selected by actual operative procedure codes related to the ventral abdominal wall. Consecutive patients with the diagnosis ventral hernia or abdominal wall defect, who consented, were included. The last repair in patients who underwent more than 1 ventral abdominal wall repair in the study period was analyzed and the other repairs were regarded previous operations.

Our department is a tertiary referral center for patients with abdominal wall defects complicated by infection, enterocutaneous fistula, loss of domain, and severe comorbidity. Therefore, overall results might overestimate those obtained in an average population of ventral hernia repair. To address this potential bias, we separately analyzed all primary and secondary outcomes in a subgroup of patients who underwent repair of an uncomplicated midline incisional hernia. Uncomplicated was defined as no wound infection, no enterocutaneous fistula, and no further surgical procedure at repair.

Outcome Measures

Primary outcome was the incidence of inadvertent enterotomy. Inadvertent enterotomy was defined as every iatrogenic unintended full-thickness bowel defect detected during operation.

Bowel defects from preexisting fistulas or created while dissecting the bowel loop that harbored the fistula were not scored as inadvertent enterotomy.

Secondary outcomes were a delayed diagnosed perforation (DDP), the occurrence of serious adverse events (SAEs), and health care utilization. DDP was defined as a bowel defect with spill of gastrointestinal content that was diagnosed postoperatively by imaging, at reoperation or at autopsy, and which was not explained by anastomotic leakage or bowel ischemia.

SAEs were scored for their presence and number. Postoperative complications scored as a SAE were death, wound infection, urinary tract infection, pneumonia, sepsis, anastomotic leakage, bleeding, fistula, and abscess. SAEs were diagnosed according to the criteria of the ICD-10, the National Nosocomial Infections Surveillance System, the Center for Disease Control and Prevention, or according to the opinion of the senior medical staff of the department.

Health care utilization data included the number of patients requiring urgent surgical reintervention, parental feeding and admission to the ICU, total hospital stay, and ICU stay. Medication costs were calculated according to the standardized price list by the Dutch College of Health Insurance Companies updated for June 2008. Health care utilization outcomes were analyzed for the subgroups of patients with and without enterotomy and patients with an adhesiolysis time shorter or longer than 30 minutes.

Possible Risk Variables

Demographic characteristics were gender (male, female), age (years), body mass index (BMI, kg/m2), smoking habit (smoker, ex-smoker, nonsmoker), and the Physiologic and Operative Severity Score for the enumeration of Mortality and Morbidity (P-POSSUM) (0%–100%).

Preoperative variables included use of corticosteroids, a history of peritonitis, presence of intestinal fistula, the number of previous abdominal operations, and the anatomical site of the last operation before the first hernia repair (lower abdominal, upper abdominal, gynecological, urological, and none) according to the classification used by the Surgical and Clinical Adhesions Research group.(16;21) Hernia characteristics were obtained from the patient records and operation notes and the patient history including the number of previous repairs, the type of hernia (midline, not midline), the largest diameter of the hernia (<=10 cm or >10 cm), and the type (coated, noncoated) and location (intraperitoneal, extraperitoneal) of mesh used in previous repairs. Intraoperative variables included adhesiolysis time and adhesion score according to Zühlke et al: 0, no adhesions; 1, filmy adhesions; 2, stronger adhesions requiring some sharp dissection; 3, dense vascularized adhesions requiring sharp dissection; 4, extreme dense adhesions with high risk for organ damage during dissection.(22) Patients with a Zühlke score of 3 and 4 were compared with those with a score of 0, 1, or 2.

Statistical Analysis

Univariate and multivariate regression analyses were performed to identify risk factors for all patients suffering from one or more inadvertent enterotomies and separately for the subgroup of patients with an uncomplicated midline incisional hernia. Risk factors with P <= 0.30 in univariate were selected as candidate risk factors for multivariate analysis. In multivariate analysis, a stepwise forward selection procedure was used with a P-entry <= 0.30 and P-stay <= 0.10. Discriminative value of the regression model was assessed by

determining receiver operative characteristic (ROC) curve. We calculated the incidence of enterotomies per total adhesiolysis time, expressed as the time needed to harm. Characteristics of a continuous nature were reduced to a dichotomous nature with the median as cutoff. Health care utilization and SAE data were analyzed with Kruskal-Wallis and Fisher exact tests for continuous and dichotomous characteristics, respectively. SAEs and health care data were compared between patients with and without an enterotomy and between patients with and without extensive adhesiolysis. Extensive adhesiolysis was defined by adhesiolysis time, using the methods to determine the optimal cut point for research purposes described by Magder et al.(23) This method was applied on the odds ratio (OR) for incidence of SAE with cut points rounded at 5 minutes. We used SPSS for Windows version 17.0 software (SPSS, Chicago, IL) for statistical analysis. $P < 0.05$ was considered significant.

Results

Patient Characteristics

A total of 844 planned operations were eligible for inclusion in the LAPAD study. One hundred forty-three operations met the inclusion criteria repair of ventral hernia or abdominal wall defect. Eight patients were excluded because informed consent could not be obtained. Two patients had incisional hernia repair twice in the study period, resulting in 133 patients for analysis.

Five experienced surgeons performed all abdominal wall repairs either as primary surgeon or as assisting surgeon supervising a resident. No data were missing. Fourteen (10.5%) patients underwent hernia repair by primary closure, 29 (21.8%) by component separation technique, 66 (49.6%) by mesh repair, and 24 (18.0%) by a combination of component separation technique and mesh repair. Nine patients (6.7%) underwent laparoscopic ventral hernia repair. Laparoscopy was converted in 2 (22.2%) patients, for complicated adhesiolysis in one and difficulty with fixation of the mesh in the other.

One hundred twenty-nine patients (97%) had a ventral incisional hernia, in 107 (82.9%) in the midline. Three patients (2.3%) had a parastomal hernia and one patient (0.8%) had a primary umbilical hernia. In 20 patients (15%), the hernia was complicated by enterocutaneous fistula. The hernia was larger than 10 cm in length or width in 69 (51.8%) patients.

Additional surgical procedures were done in 12 (9%) patients, a bowel resection in 3, a pancreas resection in 3, a liver resection in 3, an esophageal resection in 1, and a cholecystectomy and placement of a feeding jejunostomy each in 1 patient. Seventy-eight (58.6%) patients had an uncomplicated incisional midline hernia and formed the subgroup.

Sixty-six (47.5%) patients underwent repair of a recurrent hernia, 35 patients had one and 31 patients had multiple previous repairs. Forty-four (66.7%) patients with recurrent hernia had a mesh in situ from a previous hernia repair, 18 (40.9%) in an intraperitoneal and 26 (59.1%) in an extraperitoneal position. Most intraperitoneal meshes contained an absorbable (50.0%) or nonabsorbable (27.8%) antiadhesive layer. Fully absorbable mesh and mesh without antiadhesive properties were used in 11.1% of intraperitoneal mesh repair.

Table 1 Patients With Enterotomy and Crude ORs From Univariate Logistic Regression of Risk Factors for Inadvertent Enterotomy in the Total Group

	Inadvertent Enterotomy		**Univariate Analysis**		
	Yes	**No**	**OR**	**95% CI**	**P**
Demographics					
Gender					
• Male	11 (12.8%)	11 (87.2%)	Ref.		
• Female	6 (12.8%)	6 (87.2%)	1.00	0.34-2.90	.998
Age* (each year increase)	62 ± 11.9	58.5 ± 12.1	1.03	0.98-1.08	.267
BMI* (kg/m^2, each point increase)	25.8 ± 3.3	27.9 ± 5.1	0.90	0.79-1.02	.098
Smoking					
• Non smoker	5 (11.1%)	40 (88.9%)	Ref.		
• ex-smoker	10 (16.7%)	50 (83.3%)	1.60	0.51-5.06	.424
• smoker	2 (7.4%)	25 (92.6%)	0.64	0.12-3.55	.610
Patient history					
Previous hernia corrections					
• None	8 (11.9%)	59 (88.1%)	Ref.		
• One	4 (11.4%)	31 (88.6%)	0.95	0.27-3.41	.94
• Multiple	5 (16.1%)	26 (83.9%)	1.42	0.42-4.75	.57
Number of previous operations† (each number increase)	4 (2 - 7)	3 (0 - 14)	1.15	0.93-1.41	.193
Surgical experience					
• Surgeon	11 (13.6%)	70 (86.4%)	Ref.		
• Resident	6 (11.5%)	46 (88.5%)	0.83	0.29-2.40	.731
P-Possum score* (% increase)	4.0 ± 5.3	3.4 ± 6.9	1.01	0.95-1.10	.704
Corticosteroid use					
• No	17 (13.4%)	110 (86.6%)	Ref.		
• Yes	0 (0%)	6 (100%)	0.00	0.00-NA	>.999
Peritonitis in history					
• No	12 (11.7%)	91 (88.3%)	Ref.		
• Yes	5 (16.7%)	25 (83.3%)	1.52	0.49-4.71	.471
Index operation					
Lower abdominal	10 (13.5%)	64 (86.5%)	Ref.		
• Upper abdominal	4 (11.1%)	32 (88.9%)	0.80	0.23-2.75	.800
• Gynecological	2 (15.4%)	11 (84.6%)	1.16	0.22-6.04	.857
• Urological	1 (11.1%)	8 (88.9%)	0.84	0.09-7.10	.800
• None	0 (0%)	1 (12.8%)	0.00	0.00-NA	>.999
Operative characteristics					
Type of hernia					
• Other	2 (6.5%)	29 (93.5%)	Ref.		
• Median	15 (14.7%)	87 (85.3%)	2.50	0.54-11.59	.242
Adhesiolysis time* (each minute increase)	66.9 ± 32.4	31.1 ± 26.6	1.03	1.02-1.05	<.001
Zühlke score					
• ≤ 2	8 (9.6%)	75 (90.4%)	Ref.		
• > 2 ‡	9 (18.0%)	41 (82.0%)	2.06	0.73-5.73	.168
Mesh in situ					
• no	9 (10.1%)	80 (89.9%)	Ref.		
• yes	8 (18.2%)	36 (81.8%)	1.95	0.70-5.47	.204
Fistula					
• No	10 (8.8%)	103 (91.2%)	Ref.		
• Yes	7 (35.0%)	13 (65%)	5.55	1.80-17.08	.003
Size					
• ≤10cm	2 (3.1%)	62 (96.9%)	Ref.		
• >10cm	15 (21.7%)	54 (78.3%)	8.61	1.88-39.37	.005

Values are ∗mean (SD) or †median (range).

‡Zühlke score > 2 in operative area and under scar.

Ref indicates reference.

The anatomical area of the initial operation was lower abdominal in 74 (55.6%), upper abdominal in 36 (27.1%), gynecological in 13 (9.8%), and urological in 9 (6.8%) patients. One patient with umbilical hernia (0.8%) had no prior surgery (Table 1).

Inadvertent Enterotomy, DDP, and Adhesiolysis Time

A median number of 1 (range 1–9) enterotomies occurred in 17 of 133 patients (12.8%). Eleven patients had small bowel enterotomies, 4 had large bowel enterotomies, and 2 patients had enterotomies in both small and large bowel. DDP occurred in 2 patients, one in whom also an enterotomy was detected during surgery. There were no enterotomies or DDPs in the laparoscopic group.

Surgical history was comparable between patients with and without an enterotomy. Nine (52.9%) patients with enterotomy had a previous abdominal wall defect repair compared with 47 (49.1%) patients without enterotomy; the number of patients with multiple repairs were 5 and 26, respectively (P = 0.814).

Enterotomies were made during the opening of the abdominal cavity in 4 patients. Two patients suffered enterotomies both during opening of the abdominal cavity and during subsequent adhesiolysis deeper in the abdominal cavity or along the peritoneal side walls. The remaining 11 patients had enterotomies after opening of the abdominal cavity, in 6 of them following resection of a previously placed mesh.

Adhesiolysis was done in 124 patients (93.2%). Mean (± SD) adhesiolysis time was 66.9 ± 32.4 minutes in patients with enterotomy versus 31 ± 26.6 minutes in patients without enterotomy (P < 0.001). Thirty-three inadvertent enterotomies were caused in 4750 minutes of adhesiolysis, corresponding with a cumulative incidence of 1 enterotomy after every 144 minutes of adhesiolysis. Adhesiolysis times were comparable for patients with intraperitoneal mesh, extraperitoneal mesh, or no mesh in situ (35.1 ± 26.8 minutes, 39.4 ± 32.0 minutes, and 34.8 ± 30 minutes, respectively; P = 0.747).

Tenacity of adhesions was high with 85 (63.9%) patients having Zühlke scores more than 2 under the scar and 75 (56.4%) further away. Extreme dense adhesions (Zühlke score 4) were found under the scar in 27 (20.3%) patients and at the operative areas in 26 (19.5%) patients. Fifty (37.6%) patients had dense adhesions both under the scar and distant of the scar.

Adhesiolysis time, the presence of a fistula, and hernia size greater than 10 cm were significant risk factors in the univariate analysis (Table 1). These and the factors age, BMI, the number of previous abdominal operations, a midline hernia, and the presence of mesh, with a P < 0.30, were included in the multivariate analysis. Subdivision of the location of the mesh (ie, intraperitoneal or extraperitoneal) was not presented in the final multivariate analysis because it did not result in any significant changes and did not improve the model (intraperitoneal vs extraperitoneal mesh, OR 0.84; 95% CI 0.17-4.0-7; P = 0.828).

Multivariate stepwise regression analysis revealed adhesiolysis time as independent and significant risk factor for incidence of inadvertent enterotomy [OR (95% confidence Interval [CI]) 1.03 (1.01–1.05) for each minute increase in adhesiolysis time]. There was a trend toward a higher incidence of enterotomy in patients with mesh in situ and a hernia size greater than 10 cm. A trend toward a lower incidence was found in patients with higher BMI (Table 2). The area under the ROC curve of the multivariate model was 0.87 (95% CI 0.79–0.96).

Table 2 Adjusted ORs From Stepwise Multivariate Logistic Regression of Risk Factors for Inadvertent Enterotomy in the Total Group and Subgroup

	Total group				**Subgroup**		
	OR	**95% CI**	**P**		**OR**	**95% CI**	**P**
Demographics							
Age (each year increase)	NS	NS	NS		NA	NA	NA
BMI (kg/m^2, each point increase)	0.86	0.72-1.02	.076		NA	NA	NA
Patient history							
Number of previous operations (each n increase)	NS	NS	NS		NS	NS	NS
Operative characteristics							
Type of hernia (median *vs* other)	NS	NS	NS		NA	NA	NA
Adhesiolysis time (each minute increase)	1.03	1.01-1.05	.004		1.04	1.02-1.07	.002
Zühlke score (>2 *vs* ≤2)	NS	NS	NS		NS	NS	NS
Mesh in situ (yes *vs* no)	3.28	0.93-11.61	.066		7.371	1.03- 53.0	.047
Fistula (yes *vs* no)	NS	NS	NS		NA	NA	NA
Size (>10cm *vs* ≤10cm)	5.19	0.97-27.68	.054		NS	NS	NS

NS: not selected for model in stepwise multivariate analysis.
NA: not applicable as candidate risk factor in the subgroup analysis (P > 0.30 in univariate).

Eight (10.3%) patients had a median of one enterotomy (range 1–9) in the subgroup of patients with uncomplicated midline incisional hernia. Again, adhesiolysis time was a significant risk factor in univariate analysis with an OR 1.04 (95% CI 1.02–1.07; P = 0.002) for each minute increase in adhesiolysis time. There was a trend toward increased enterotomy incidence in patients with mesh present [mesh 5/25 (20%) vs no mesh 3/53 (5.7%); OR 4.2; 95% CI 0.9–19.1; P = 0.066]. In multivariate analysis, adhesiolysis time and mesh presence were significant risk factors (OR 1.05; 95% CI 1.02–1.09; P = 0.004 and OR 7.4; 95% CI 1.0–53.0; P = 0.047, respectively). The area under the ROC curve was 0.90 (95% CI 0.81–0.98).

Impact of Enterotomy

Eight (47.1%) patients with an enterotomy underwent enterectomy. Bowel resection in patients without enterotomy was mostly done as part of resection of an enterocutaneous fistula. There were no anastomotic leakages related to bowel resection for enterotomy. Two patients (1.5%) died during hospital admission; one of these patients had experienced an enterotomy and a DDP. Cause of death was hemorrhage after a long and complicated ICU stay. The other patient died from pneumonia.

Patients with an inadvertent enterotomy experienced significantly higher rates of complications requiring urgent surgical reintervention and parenteral feeding (38.9% vs 12.9%; P = 0.029 and 35.6% vs 13.8%; P = 0.037, respectively) than patients without an enterotomy (Table 3). Total hospital stay of patients with enterotomy was significantly longer (20.8 ± 35.0 vs 8.6 ± 10.6 days, P = 0.002) and costs of in-hospital prescribed medication were higher (€1178 ± 3207 vs €250 ± 475, P < 0.001). The increase in medication costs was mainly due to increased use of intravenous antibiotics.

Table 3 Impact of Adhesiolysis Complicated by Enterotomy on Clinical Outcomes and Costs.

Outcome	**Enterotomy** (n=17)	**No enterotomy** (n=116)	***P***
Patients with			
SAE (n)	7 (41.2%)	32 (27.6%)	.264
Sepsis	2 (11.8%)	2 (1.7%)	.079
Wound infection	2 (11.8%)	9 (7.8%)	.632
Abscess/ fistula/ leakage	2 (11.8%)	3 (2.6%)	.122
Urinary tract infection	1 (5,6%)	5 (4.3%)	.567
Pneumonia	3 (17.6%)	15 (12.9%)	.702
Hemorrhage	1 (5.9%)	10 (8.6%)	>.999
Death	1 (5.9%)	1 (0.9%)	.240
ICU admissions (n)	5 (29.4%)	17 (14.7%)	.159
Reinterventions (n)	6 (35.3%)	15 (12.9%)	.029
Parenteral feeding (n)	6 (35.3%)	16 (13.8%)	.037
Hospital stay (days)	20.8 ± 35.0*	8.6 ± 10.6*	.002
ICU stay (days)	10.7 ± 36.2*	1.0 ± 4.0*	.096
Medication costs (€)	1178 ± 3207*	250 ± 475*	<.001

*Means ± SD

In 6 (35%) patients with an enterotomy but no gross spillage of intestinal content, an extraperitoneal mesh was placed during hernia repair. In one of the patients, the mesh was removed 2 days after surgery in an acute setting because of a DDP. In another patient, the mesh was removed after 3 months because of fistula formation. One patient presented at the emergency department 2 weeks postoperatively with wound infection, but no excision of mesh was required. The other 3 patients did not suffer from any complications.

Optimal cut point for extensive adhesiolysis was 30 minutes. Sixty-three (47.4%) patients had an adhesiolysis time longer than 30 minutes, and these patients had significantly more complications than those with adhesiolysis time shorter than 30 minutes (38.1% vs 21.4%; P = 0.038). Patients with adhesiolysis more than 30 minutes experienced a significantly higher rate of sepsis (6.3% vs 0%; P = 0.048), wound infection (14.3% vs 2.9%; P = 0.025), and abdominal complications (fistula, abdominal abscess, and anastomotic leakage; 7.9% vs 0%; P = 0.022) than those with an adhesiolysis less than 30 minutes (Table 4). Excluding patients with an enterotomy or DDP, adhesiolysis of 30 minutes or longer still was associated with a higher number of ICU admissions (25.0% vs 7.4%; P = 0.015), a greater need for parenteral feeding (29.2% vs 2.9%; P < 0.001), a longer total hospital stay (12.8 ± 14.7 vs 5.6 ± 4.5 days; P = 0.001) and ICU stay (2.1 ± 5.9 vs 0.2 ± 1.2 days; P = 0.006) and higher costs from in-hospital prescribed medication (€421 ± 644 vs €129 ± 248; P < 0.001).

Table 4 Impact of Adhesiolysis (≥30 min) on Clinical Outcomes and Costs in the Total Group

Outcome	**Adhesiolysis <30 min** (n=70)	**Adhesiolysis ≥30 min** (n=63)	***P***	**Adhesiolysis ≥30 min** ***No enerotomy, no DDP*** (n=48)	***P***
Patients with					
SAE (n)	15 (21.4%)	24 (38.1%)	.038	17 (35.4%)	.141
Sepsis	0 (0%)	4 (6.3%)	.048	2 (4.2%)	.169
Wound infection	2 (2.9%)	9 (14.3%)	.025	7 (14.6%)	.032
Abscess/ fistula/ leakage	0 (0%)	5 (7.9%)	.022	3 (6.2%)	.068
Urinary tract infection	1 (1.4%)	5 (7.9%)	.101	4 (8.3%)	.158
Pneumonia	7 (10%)	11 (17. 5%)	.310	8 (16.7%)	.402
Hemorrhage	6 (8.6%)	5 (7.9%)	>.999	4 (8.3%)	>.999
Death	1 (1.4%)	1 (1.6%)	>.999	0 (0.0%)	>.999
ICU admissions (n)	5 (7.1%)	17 (27.0%)	.002	12 (25.0%)	.015
Reinterventions (n)	5 (7.1%)	16 (25.4%)	.004	10 (20.8%)	.048
Parenteral feeding (n)	2 (2.9%)	20 (31.7%)	.001	14 (29.2%)	<.001
Hospital stay (days)	5.6 ± 4.5*	15.2 ± 22.2*	<.001	12.8 ± 14.7*	<.001
ICU stay (days)	0.2 ± 1.2*	4.5 ± 22.2*	.002	2.1 ± 5.9*	.006
Medication costs (€)	128 ± 244*	636 ± 1754*	<.001	421 ± 644*	<.001

*Means ± SD

In the subgroup of 78 patients with an uncomplicated incisional hernia, no significant differences in the incidence of SAEs could be found between enterotomy and no enterotomy (Table 5). The 8 patients with enterotomy had a longer hospital stay (26.0 ± 51.4 vs 17.4 ± 10.7 days; P = 0.030) and higher medication costs (€1887 ± 4690 vs €215 ± 395; P = 0.030) compared with those without enterotomy. Patients with adhesiolysis time longer than 30 minutes were admitted more frequently to the ICU (22.9% vs 4.7%; P = 0.037), had longer ICU stay (5.8 ± 25.5 vs 0.2 ± 1.1 days; P < 0.001), a longer total hospital stay (14.7 ± 28.0 vs 4.9 ± 2.9 days; P < 0.001), and higher medication cost (€720 ± 228 vs €114 ± 176; P < 0.001).

Table 5 Impact of Adhesiolysis Complicated by Enterotomy and of Adhesiolysis (≥30 min) on Clinical Outcomes and Costs in the Subgroup

Outcome	**Adhesiolysis <30 min** (n=43)	**Adhesiolysis ≥30 min** (n=35)	***P***		***No enterotomy*** *(n=70)*	***enterotomy*** (n=8)	***P***
Patients with							
SAE (n)	11 (25.6%)	9 (25.7%)	>.999		17 (24.3%)	3 (37.5%)	.416
Sepsis	0 (0.0%)	2 (5.7%)	.198		1 (1.4%)	1 (12.5%)	.196
Wound infection	1 (2.3%)	2 (5.7%)	.585		2 (2.9%)	1 (12.5%)	.280
Abscess/ fistula/ leakage	0 (0.0%)	1 (2.9%)	.449		0 (0%)	1 (12.5%)	.103
Urinary tract infection	1 (2.3%)	1 (2.3%)	.585		3 (4.3%)	0 (0%)	>.999
Pneumonia	6 (14.0%)	5 (14.3%)	>.999		9 (12.9%)	2 (25.0%)	.314
Hemorrhage	3 (7.0%)	2 (5.7%)	>.999		4 (5.7%)	1 (12.5%)	.427
Death	1 (2.3%)	1 (2.9%)	>.999		1 (1.4%)	1 (12.5%)	.196
ICU admissions (n)	1 (2.3%)	5 (14.3%)	.037		8 (11.4%)	2 (25.0%)	.271
Reinterventions (n)	3 (7.0%)	6 (17.1%)	.285		7 (10.0%)	2 (25.0%)	.229
Parenteral feeding (n)	1 (2.3%)	5 (14.3%)	.084		5 (7.1%)	1 (12.5%)	.496
Hospital stay (days)	4.9 ± 2.9*	14.7 ± 28.0*	<.001		17.4 ± 10.7*	26.0 ± 51.4*	.212
ICU stay (days)	0.20 ± 1.1*	5.8 ± 25.5*	<.001		0.73 ± 3.0*	20.1 ± 52.6*	.030
Medication costs (€)	114 ± 176*	720 ± 228*	<.001		215 ± 395*	1887 ± 4690*	.030

*Means ± SD

Discussion

Open abdominal wall hernia repair is associated with extensive adhesiolysis leading to inadvertent organ damage in about 1 of 8 patients. Adhesiolysis time, most likely reflecting the difficulty of the repair procedure, was a significant and independent risk factor for enterotomy both in the whole group and in patients with uncomplicated midline incisional hernia. Adhesiolysis complicated by enterotomy and a long during adhesiolysis adversely affected important clinical and socioeconomic aspects of patient convalescence.

The incidence of enterotomy was unexpectedly high. Jenkins et al evaluated laparoscopic repairs of 69 recurrent hernias and found only 3% patients with an enterotomy.(24) In a recent study, Wara et al found a 4% incidence of enterotomy during laparoscopic repair of 72 parastomal hernias. (25) In a large cohort of 114 laparoscopic hernia and 1009 open hernia repairs, 8% and 7% enterotomies, respectively, were reported.(9) The higher rate in the present study most likely reflects a more difficult patient population as may be concluded from the small proportion of laparoscopic repairs and the high proportion of patients with complex hernia and comorbidity. One in 6 patients had a fistula at the time of hernia repair and almost all surgeries were (clean-) contaminated. More complexity, however, does not fully explain the high incidence because uncomplicated midline incisional hernia repair still had a 10% enterotomy rate. Perhaps the lower incidence of enterotomies reported in laparoscopic hernia repair is an underestimate because delayed bowel perforation was not included in those series.(12;20;26) Delayed detection of operative bowel injury seems to occur more frequently in laparoscopic than in open repair and is associated with marked morbidity and mortality.(12)

The prospective nature of the study enabled us to accurately evaluate adhesiolysis-related factors predicting an enterotomy. Adhesiolysis time was found to be a strong predictor for enterotomy in both complicated and uncomplicated hernia repair; a large defect and mesh presence were weak predictors. Obviously, adhesiolysis time cannot be accurately predicted before operation. The finding of enterotomy associated with adhesiolysis time, however, is of value during patient counseling for informed consent.

Highly dense adhesions are prone for inadvertent injury when lysed. Yet, the impact of tenacity on enterotomy risk was not significant in our study. The scoring of adhesion tenacity was an estimate because adhesion tenacity varied between adhesions in the abdomen and adhesion quantity was not assessed. This likely explains the lack of significance of the single variable tenacity. Adhesiolysis time encompasses tenacity and quantity of adhesions and better reflects the complexity of adhesiolysis.

In a previous retrospective study from our group that predominantly included repeat colorectal surgeries and revealed a risk for enterotomy of 19%, one third of enterotomies occurred at abdominal entry.(13) In that series, lower pelvis adhesiolysis had the highest risk for enterotomy, which is an area not commonly dissected in ventral hernia repair. The number of previous laparotomies predicted the risk of enterotomy, a finding not reproduced in the present series. Most likely, the percentage of multiple recurrent hernia repairs (<25%) was too low to allow appropriate analysis.

The attendance of an observer in the operating room might have raised vigilance of surgeons to meticulously do adhesiolysis and avoid bowel opening. This would imply that the enterotomy incidence would be higher when unobserved. We noticed, however, that the operating team became rapidly habituated to the presence of an observer during the study period of 2 years. So, the observer effect seems limited.

We introduced the “adhesiolysis time needed to harm” in this analysis. This outcome measure does not provide a better understanding of the patient's individual risk but gives a qualitative assessment of the difficulty surgeons face while cutting adhesions in a homogeneous group of patients. Calculation of the “time needed to harm” might facilitate comparison between studies of factors that influence the difficulty of adhesiolysis and has value for health economists involved in cost price calculation of surgical interventions.

Halm et al reported a significant difference in bowel resection between patients with intraperitoneal mesh (21%) and those with extraperitoneal mesh (0%) and related this observation to bowel injury cutting adhesions between bowel and mesh.(17) We found a higher incidence of enterotomy with mesh regardless of intraperitoneal or extraperitoneal mesh position. Notably, antiadhesive coatings were used in 4 of 5 patients with intraperitoneal mesh in our series, and the majority of meshes in Halm's study were made of nonabsorbable polypropylene. One should also be cautious to take bowel resection as a measure of adhesion severity and injury after adhesiolysis as Halm et al did. Only half of our patients with enterotomy required bowel resection. In a recent large retrospective study of 1444 patients in 16 Veterans Affairs hospitals examining the effect of repair type and technique on the difficulty and complications of subsequent surgery (two-third rerepair of ventral hernia), no significant effect of repair type, mesh type, or position on risk of inadvertent enterotomy was demonstrated.(27) These results correspond with our findings indicating that extraperitoneal mesh position does not prevent adhesiolysis-induced injury. We have regularly encountered a peritoneal protrusion of an extraperitoneal mesh with adhesive attachments giving similar operative difficulty as an intraperitoneal mesh at rerepair. One might speculate to use antiadhesive meshes when placed in the extraperitoneal space after open abdominal wall repair on the basis of the assumption that the peritoneal layer takes part in the inflammatory response elicited by the surgery and the foreign body implanted and becomes adhesiogenic.

Placing a mesh in a contaminated environment is known to increase the risk of mesh infection and fistula formation.(28) In a retrospective cohort of 42 mesh infections, early infection correlated with DDP.(29) Half of the patients in our study who received a mesh after an inadvertent enterotomy was repaired suffered from complications, even though there was no gross spillage from the enterotomy and meshes were not placed in the intraperitoneal cavity. The difficult and long adhesiolysis rather than the enterotomy probably accounts for the mesh-related complications. Our limited data of patients with enterotomy and mesh placement suggest avoiding mesh repair after long during complicated adhesiolysis.

Patients with adhesiolysis complicated by enterotomy had a significantly higher incidence of unplanned bowel resection, sepsis, urgent reoperation, parenteral feeding, and prolonged hospital stay underlining the huge impact of inadvertent enterotomy on postoperative complications. The results accord with those of a previous retrospective study of all types of reoperations from our department.(13) A new finding is the higher incidence of postoperative surgical complications, the longer hospital stay, and increased medication costs after more

than half an hour of adhesiolysis. This finding was independent of enterotomy occurrence or complexity of the abdominal wall defect. In a large prospective randomized study of 1701 patients undergoing colorectal resection for benign causes, every 30 minutes of adhesiolysis was correlated with an increase of postoperative stay by 1 day.(30) This and our results demonstrated the large adverse effect of adhesiolysis time alone on morbidity and health care utilization.

Prolonged adhesiolysis and adhesiolysis complicated by bowel injury introduced high direct hospital costs given the twofold increase in hospital stay, the higher number of patients needing ICU treatment, the higher number of reoperations, and the almost fivefold increase in medication costs. Available literature on the socioeconomic burden of adhesions has focused only on direct hospital costs caused by adhesive small bowel obstruction. In a recent study, Wilson et al estimated the cumulative costs of readmission for adhesive small bowel obstruction after abdominal surgery at €960 per patient.(31) Comparison has not been done, but we speculate that the costs of adhesiolysis and subsequent inadvertent organ damage are higher than those of adhesive small bowel obstruction.

Although adhesiolysis-related organ damage is common during repeat surgery and accounts for a huge burden of morbidity, it is one of the most neglected and poorly investigated complications of abdominal surgery. This is the first large prospective cohort study giving detailed information on the morbidity of adhesions in open abdominal wall repair. Although our series encompass patients with complex abdominal wall defects, most findings were similar for relatively simple midline ventral incisional hernias. Therefore, the results are representative for open ventral hernia repair.

This study provides the first important epidemiological data on incidence, predictive factors, and impact of adhesiolysis in surgical repair of abdominal wall defects. The high incidence and large impact of adhesions emphasizes the need for adhesion prevention in all abdominal surgeries potentially complicated by a hernia. Unfortunately, only a minority of surgeons routinely use antiadhesion barrier.(32) Use of antiadhesive coating on meshes is recommended when repairing a ventral wall hernia to reduce bowel adherence to the mesh with fistula formation and troublesome separation of viscera from the intraperitoneal mesh at recurrent hernia repair.(17;33;34)

Having established in a prospective way the incidence and intra- and postoperative burden of adhesions in ventral hernia repair, surgeons can properly inform their patients before consent. In addition, hospitals, health care economists, insurances companies, and manufacturers of hernia meshes may use these findings for organizational and economic purposes and cost–benefit analyses.

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Part II: difficulties of adhesions during reoperations

Chapter 7: Preoperative nomogram to predict risk of bowel injury during adhesiolysis

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Published in: British Journal of Surgery. 2014;101;720-7

Abstract

Background

Inadvertent bowel injury during adhesiolysis is a major cause of increased morbidity and mortality following abdominal surgery. Identification of risk factors predicting this complication would guide preoperative counselling and surgical decision-making. The aim of this study was to identify predictive preoperative factors for inadvertent bowel injury occurring during adhesiolysis.

Methods

All patients undergoing elective abdominal surgery between June 2008 and June 2010 were evaluated prospectively as part of the LAPAD study. Data on adhesiolysis and inadvertent organ injury were gathered by direct observation during operation. Univariable logistic regression was used to investigate factors that increased the risk of inadvertent bowel injury. Independent predictors of bowel injury were identified using multivariable logistic regression and used to create a clinical nomogram.

Results

Of 715 patients eligible for analysis, 48 (6.7 per cent) had inadvertent bowel injuries. In 42 patients the defect was detected during operation and in nine at a later time (3 patients had both). Bowel resection was required for almost two-thirds of the enterotomies. The number of previous laparotomies, anatomical site of the operation, presence of bowel fistula and laparotomy via a pre-existing median scar were independent predictors of bowel injury. A clinical scoring system was constructed using a nomogram incorporating these risk factors; this had a predictive discrimination, measured as the area under the receiver operating characteristic curve, of 0.85.

Conclusion

A nomogram based on four independent factors predicted the risk of inadvertent bowel injury. Registration number: NCT01236625 (http://www.clinicaltrials.gov).

Introduction

Adhesion formation is the most important long-term complication of abdominal surgery, with a lifelong risk of developing a variety of clinical conditions including small bowel obstruction, infertility and chronic pain.(1;2) A possibly more important consequence of adhesion formation is the difficulty encountered during repeat surgery.(3;4) Adhesiolysis increases operating time and has an adverse effect on the patient's convalescence, especially if a bowel injury occurs.(5-7) The incidence of accidental bowel injury is as high as 10–20 per cent in patients undergoing adhesiolysis.(4;6) The sequelae of bowel injury include unplanned bowel resections, an increase in the incidence of surgical complications, admission to an intensive care unit and even an increase in mortality. The mortality rate from bowel injury is estimated at between 8 and 50 per cent, depending on whether or not the defect was recognized during the operation.(4-6;8;9)

The authors have demonstrated previously that bowel injuries occur more often in patients who require extensive adhesiolysis, those with high adhesion scores or a history of multiple laparotomies, and patients who have had lower abdominal procedures.(4;6;7) Most of these factors are not known before operation, but become apparent during the procedure. Estimating the risk of adhesiolysis-related complications, based on preoperative variables, would enable the risks and benefits of surgery for the individual patient to be taken into consideration; this information could be used during counselling, and to identify those who might benefit from the use of adhesion barriers.(10;11)

The aim of this study was to define preoperative predictors of bowel injury from data collected in a large prospective cohort of patients undergoing elective abdominal surgery. The authors also investigated whether a meaningful clinical scoring system could be developed to predict the risk of bowel injury.

Methods

This prospective observational study was carried out as part of the LAParotomy or LAParoscopy and Adhesiolysis (LAPAD) study (registration number NCT01236625; http://www.clinicaltrials.gov). The manuscript was written in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.(12) Detailed information on the LAPAD methods has been published previously.(4;7) The executive board of the institutional review board confirmed that the study was exempt from its approval. The LAPAD study was designed to assess the incidence and impact of adhesiolysis on perioperative and postoperative complications.

Patient inclusion and data collection

All adult patients scheduled for elective abdominal surgery between 1 June 2008 and 2 June 2010 at the Department of Surgery, Radboud University Nijmegen Medical Centre, were screened for inclusion. The inclusion criterion was an elective laparotomy or laparoscopy. Exclusion criteria were age under 18 years and mental disorder. Patients were included after giving oral and written informed consent.

Patient, surgical and medical data were assessed prospectively before, during and after hospital stay, and from the outpatient clinic for 6 months after discharge. During surgery,

detailed information on adhesions, adhesiolysis and inadvertent organ damage were collected through direct observation by a trained researcher who did not take part in the operation.

Variables analysed

Preoperative data on demographics, patient history, medication, operative risk scores and the planned procedure were extracted from the database for analysis. Demographics analysed comprised: sex, age, body mass index, smoking habits, and alcohol abuse based on the Alcohol Use Disorders Identification Test score.(13) Variables extracted from the patient's history included: laparotomies, laparoscopies, interval since last laparotomy, history of other surgery (and, if yes, what type of surgery), exploratory laparotomy, peritonitis, diabetes mellitus, inflammatory bowel disease and active malignancy. Medications included: corticosteroids, immunosuppressants, non-steroidal anti-inflammatory drugs, opioids and statins. The following operative risk scores were assessed: American Society of Anesthesiologists fitness classification, Portsmouth modification of the Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (P-POSSUM) and Revised Cardiac Risk Index. Aspects of the planned operation included: anatomical site of operation, median incision through a pre-existing scar, previous surgery at the anatomical site of the operation, resection of bowel fistula, surgical experience, operative severity, mesh for ventral hernia repair *in situ* and surgical approach.

To facilitate calculations, the variable anatomical operation site was categorized as lower gastrointestinal, abdominal wall or miscellaneous, the latter comprising upper gastrointestinal, hepatopancreatobiliary and other abdominal surgery associated with a low incidence of bowel injury.

Assessment of outcome

Bowel injury was classified as inadvertent enterotomy or a delayed diagnosis of perforation. Inadvertent enterotomy was defined as any iatrogenic unintended full-thickness bowel defect detected during operation. Pre-existing fistulas or defects created while dissecting the bowel loop that harboured the fistula were not scored as an inadvertent enterotomy.

Delayed diagnosis of perforation was defined as a bowel defect with spill of gastrointestinal content that was diagnosed after surgery by imaging, at reoperation or at autopsy, and which was not explained by anastomotic leakage, bowel ischaemia or any other obvious causes of leakage unrelated to adhesiolysis.

Statistical analysis

For patients who had undergone several operations during the study interval, the most recent procedure was analysed and the others regarded as previous operations to avoid duplication of risk factors.

Univariable logistic regression was used to study the differences in demographics, patient history, medication, operative risk scores and the planned procedure between patients with and without bowel defects. The incidence of bowel injuries and crude odds ratios (ORs) with 95 per cent confidence intervals (c.i.) were calculated. All predictors found to be significant in univariable analysis were included in a multivariable analysis. A stepwise, backwards selection procedure was used with a P entry ≤ 0.100 and P stay ≤ 0.100. The adjusted OR was calculated with 95 per cent c.i. The R^2 value was computed to assess the information gained

by addition of the co-variable(s) in the logistic regression model in comparison to a model without any co-variables. R^2 ranges between 0 and 100 per cent, with 0 per cent indicating that the prediction model explains none of the variability in the outcome data and 100 per cent indicating a perfect fit on the data.

The area under the receiver operating characteristic (ROC) curve (AUC) was used to quantify predictive discrimination. In general, these measures can be expected to be too high because the model was developed solely using the study sample, and this model would be expected to perform less adequately on a different random sample. Therefore, to evaluate the reliability of the created prediction model, an internal cross-validation was performed using bootstrap methods. The corrected R^2 and corrected AUC were calculated.

A nomogram was constructed using the multivariable prognostic model using the standard methods of the Regression Modelling Strategies package version 4.1-1 for R 2.12.0.(14) Such a nomogram can be used to predict bowel injury in an individual patient by filling in the values for each independent risk factor. The corresponding number of points can then be read from the scale presented. These are then summed to give a total point score, which is translated into a risk of enterotomy by using the two scales at the bottom of the nomogram. The 95 per cent c.i. of the predicted risk can be read from a 95 per cent c.i. plot of the estimated risks. The 95 per cent c.i. values were obtained by simulating 1000 draws for each combination of risk factors from the model's posterior distribution.

R version 2.12.0 (R Project for Statistical Computing, Vienna, Austria) was used for statistical analysis. $P < 0.050$ was considered statistically significant in all analyses.

Results

Of 844 consecutive elective operations that were eligible for inclusion, 89 were excluded for various reasons. Some 755 operations performed in 715 patients were available for analysis (Fig. 1). Most patients (62.9 per cent) were operated by one of 13 senior consultants participating in the study, 6.9 per cent by one of three junior consultants and 30.2 per cent by one of 31 residents. Bowel injuries occurred in 48 patients (6.7 per cent). In 42 patients a median of 1 (range 1–9) enterotomies was detected during the operation. A delayed perforation was diagnosed in nine patients. Three patients had both enterotomies detected during surgery and a delayed diagnosis of perforation.

A total of 73 enterotomies were detected in 42 patients. In 23 of these patients at least one of the enterotomies was made either under the incision, or during adhesiolysis between bowel and the abdominal wall. Eleven patients had an enterotomy in the left lower quadrant. The left upper quadrant and true pelvis was the location of an enterotomy in six and four patients respectively. Two patients had an enterotomy in the right half of the abdomen. Among the 42 patients with an enterotomy, the small bowel was lacerated in 28, the large bowel in nine, both small and large bowel in four, and one patient had a gastric enterotomy.

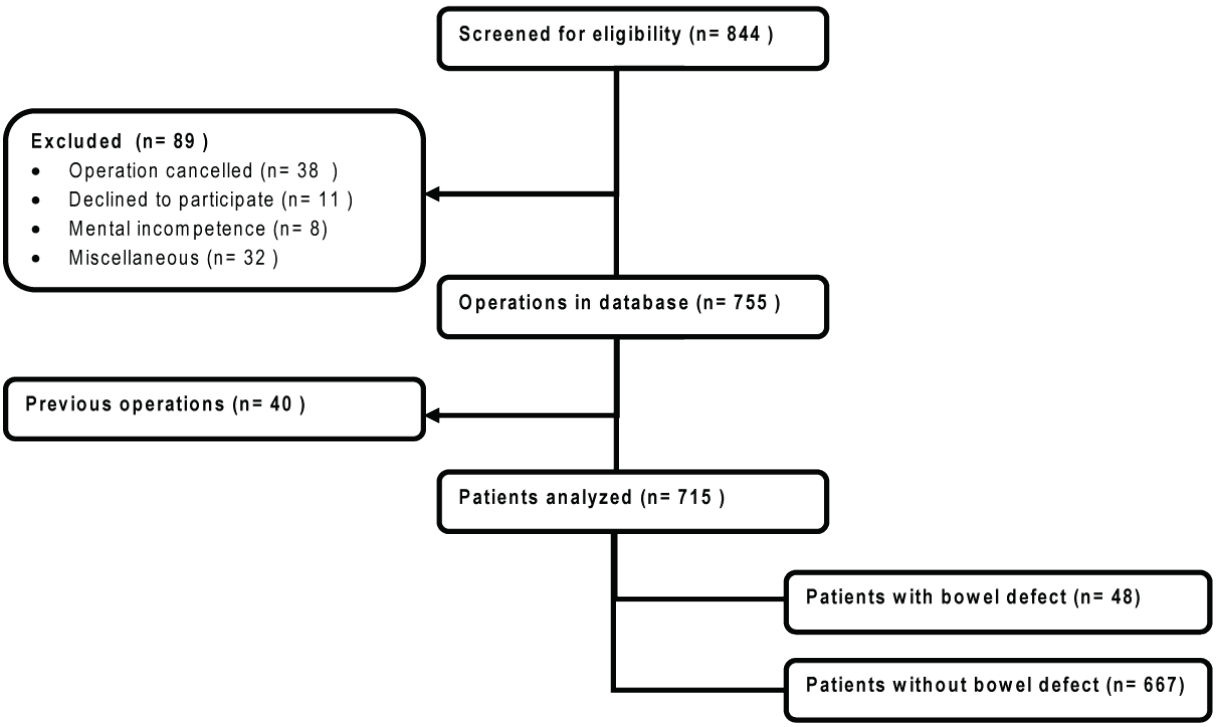

Figure 1 Flow chart of patients included in the study

Impact of bowel injury

The mortality rate was higher in the bowel injury group than among those without bowel injury: 8 per cent (4 of 48) compared with 1.9 per cent (13 of 667) respectively ($P = 0.022$). All four patients who died in the bowel injury group had been diagnosed with a delayed perforation, and two also had an enterotomy detected during operation. One patient died after 4 days from ongoing abdominal sepsis after delayed perforation; the other three died from haemorrhage following relaparotomy, pneumosepsis or acute heart failure.

Enterotomy was followed by bowel resection in 26 of 42 patients, whereas enterotomies in the remaining patients were closed primarily. Thirteen of 48 patients with bowel injury required admission to an intensive care unit. Twenty-one patients (44 per cent) had one or more serious adverse events, which included abdominal sepsis (13 per cent), wound infection (17 per cent) and pneumonia (25 per cent).

Univariable analysis of risk factors for bowel injury

In univariable analysis, the number of previous laparotomies, and a history of surgery of the lower gastrointestinal tract, abdominal wall and urogenital tract were significant risk factors for bowel injury (Table 1; Table S1, supporting information). Patients who had undergone a single laparotomy previously had only a moderately increased risk of bowel injury; this increased dramatically with additional laparotomies. The risk of bowel injury was also higher when a previous laparotomy had been carried out within the previous 6 months. Patients with active malignancy had a lower risk of bowel injuries, but also had undergone fewer laparotomies previously.

Table 1 Risk factors for bowel injury identified by univariable logistic regression analysis

	No. of patients*	Odds ratio†	*P*
Patient history			
Laparotomies			
0	2 of 263 (0.8)	1.00 (reference)	< 0.001
1	5 of 186 (2.7)	3.61 (0.69, 18.79)	0.128
2 or 3	24 of 191 (12.6)	18.75 (4.38, 80.39)	< 0.001
≥ 4	17 of 75 (23)	38.25 (8.60, 170.15)	< 0.001
Lower GI surgery			
No	9 of 378 (2.4)	1.00 (reference)	
Yes	39 of 337 (11.6)	5.37 (2.56, 11.25)	< 0.001
Abdominal wall surgery			
No	31 of 582 (5.3)	1.00 (reference)	
Yes	17 of 133 (12.8)	2.61 (1.40, 4.86)	0.003
Urological surgery			
No	36 of 635 (5.7)	1.00 (reference)	
Yes	12 of 80 (15)	2.94 (1.46, 5.91)	0.003
Active malignancy			
No	40 of 375 (10.7)	1.00 (reference)	
Yes	8 of 340 (2.4)	0.20 (0.09, 0.44)	< 0.001
Peritonitis			
No	39 of 653 (6.0)	1.00 (reference)	
Yes	9 of 62 (15)	2.67 (1.22, 5.82)	0.013
Aspects of planned operation			
Anatomical site of operation			
Miscellaneous	4 of 270 (1.5)	1.00 (reference)	< 0.001
Lower GI	28 of 327 (8.6)	6.23 (2.16, 17.99)	0.001
Abdominal wall	16 of 118 (13.6)	10.43 (3.40, 31.94)	< 0.001
Repeated median laparotomy			
No	11 of 462 (2.4)	1.00 (reference)	
Yes	37 of 253 (14.6)	7.02 (3.51, 14.04)	< 0.001
Previous surgery at anatomical site			
No	12 of 448 (2.7)	1.00 (reference)	
Yes	36 of 267 (13.5)	5.66 (2.89, 11.09)	< 0.001
Resection of fistula			
No	39 of 683 (5.7)	1.00 (reference)	
Yes	9 of 32 (28)	6.46 (2.80, 14.90)	< 0.001
Mesh *in situ*			
No	40 of 672 (6.0)	1.00 (reference)	
Yes	8 of 43 (19)	3.61 (1.57, 8.30)	0.002

Values in parentheses are *percentages and †95 per cent confidence intervals. GI, gastrointestinal. A full list of variables evaluated in the univariable analysis can be found *Table S1* (supporting information).

A previous laparoscopy had no significant effect on the risk of bowel injury. The risk of enterotomy was highest in patients scheduled for surgery of the abdominal wall and lower gastrointestinal tract. The risk also increased when surgery was planned using a median incision through a pre-existing scar, was at the same anatomical location as previous operations, required fistula resection, or a mesh was *in situ* from a previous ventral hernia repair. None of the demographic variables, medications or operative risk scores had a significant effect on the risk of bowel injury (Table S1, supporting information).

Multivariable analysis of risk factors for bowel injury

In the multivariable analysis, four predictors were included in the final model (Table 2). A history of laparotomies was the strongest predictor of bowel injury, the risk increasing with each additional laparotomy. The anatomical site of planned surgery also had an independent impact on the risk of bowel injury. Other variables included in the multivariable model were fistula resection and a median incision through a pre-existing scar.

The AUC as a measurement of the predictive discrimination of the model was 0.85 and the R^2 value was 25.8 per cent. After internal validation using bootstrapping, the AUC was 0.82 and R^2 was 20.7 per cent.

A nomogram was constructed to calculate the risk of bowel injury (Fig. 2) and 95 per cent c.i. of the predicted risk calculated (Fig. 3). Several clinical examples of how the model can be applied are provided in Table S3 (supporting information).

Table 2 Adjusted risk of bowel injury in multivariable logistic regression analysis

	Adjusted odds ratio	*P*
History of laparotomies		
0	1.00 (reference)	< 0.001
1	2.27 (0.40, 12.97)	0.355
2 or 3	10.03 (2.04, 49.24)	0.005
≥ 4	15.79 (2.97, 83.91)	0.001
Anatomical site of operation		
Miscellaneous	1.00 (reference)	0.050
Lower GI	3.81 (1.26, 11.55)	0.018
Abdominal wall	2.57 (0.78, 8.44)	0.120
Fistula surgery		
No	1.00 (reference)	
Yes	2.34 (0.95, 5.74)	0.064
Repeat median laparotomy		
No	1.00 (reference)	
Yes	1.99 (0.89, 4.44)	0.094

Values in parentheses are 95 per cent confidence intervals. GI, gastrointestinal.

Discussion

This study identified four predictors of adhesiolysis-related bowel injury. Using the nomogram built on this prediction model, the risk of inadvertent bowel injury can be estimated for an individual patient. The risk estimate can be used to inform the patient about their risk of bowel injury during adhesiolysis when obtaining informed consent. In addition, the surgeon can use the information to weigh up the benefits and risks of surgery. The prediction model demonstrated good internal validation, with comparable AUC and R^2 values after bootstrapping. The predicted risks of bowel injury ranged from 0 to 50 per cent.

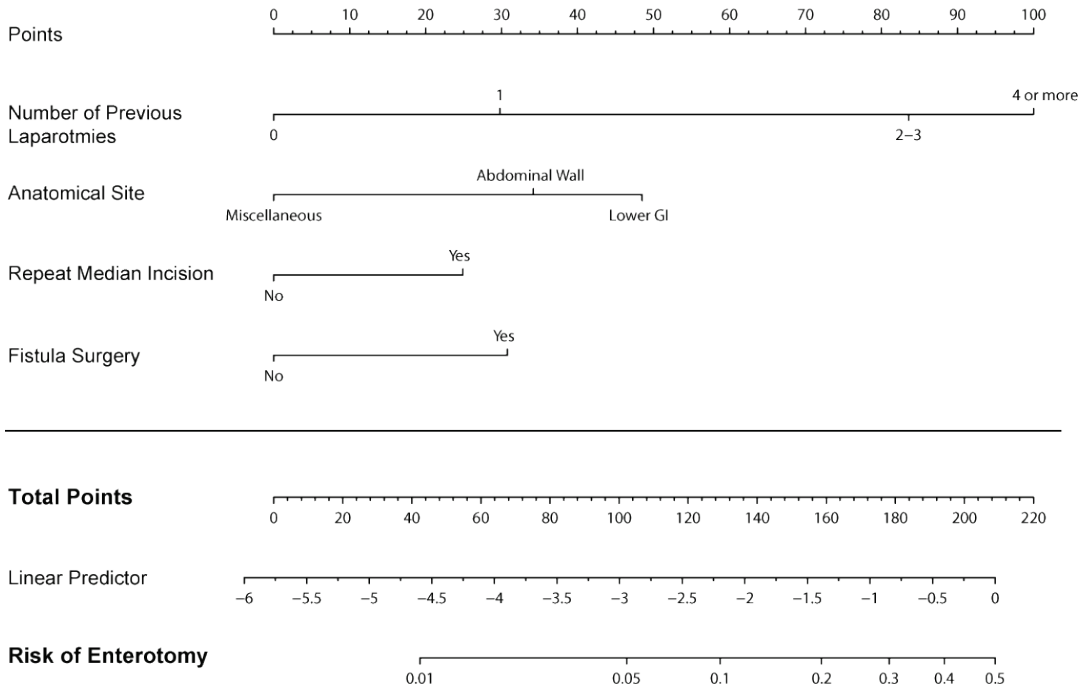

Figure 2 Nomogram to calculate the risk of enterotomy.

Draw a vertical line for each variable to the 'points' axis at the top. Sum the points for the four variables and locate this total score on the 'total points' axis. Draw a vertical line from this through the bottom two scales to determine the linear predictor and the predicted risk of enterotomy. GI, gastrointestinal

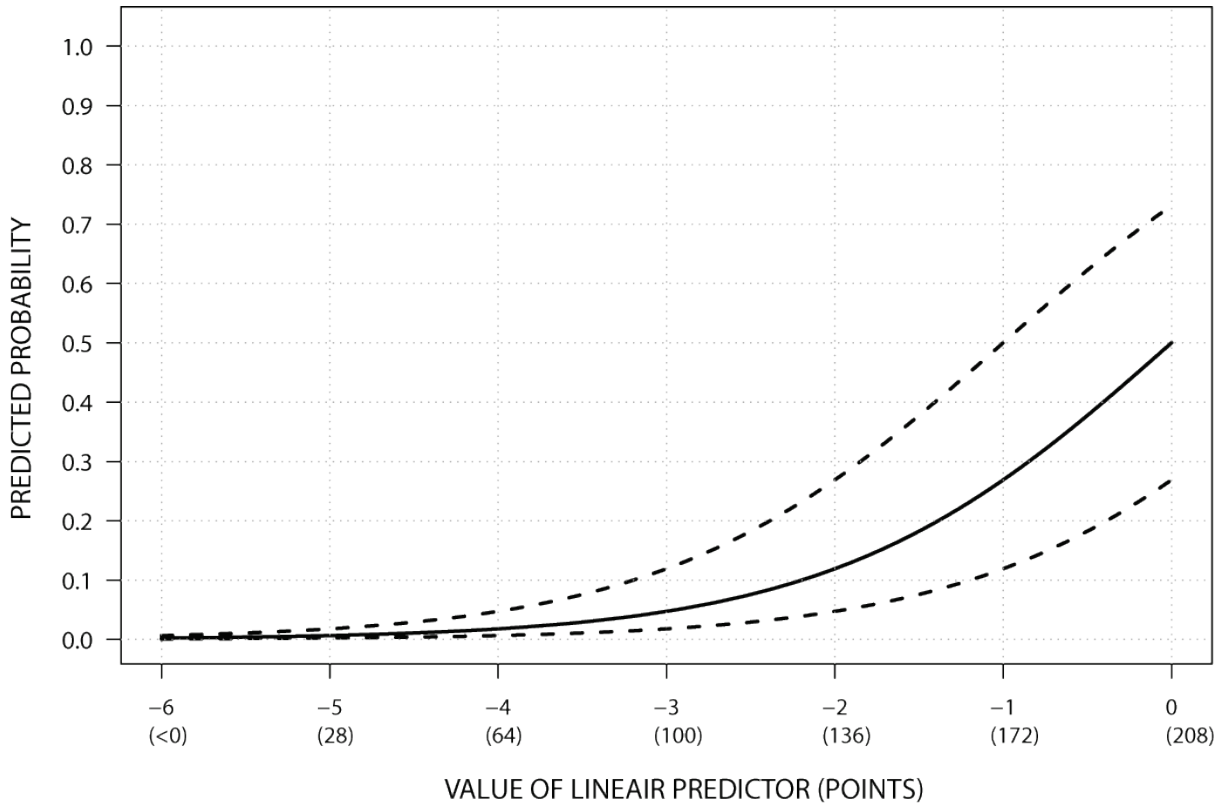

Figure 3 The predicted risk of enterotomy and 95 per cent confidence interval obtained by simulation

This large prospective cohort study was designed specifically to assess complications of adhesiolysis by direct observation, thereby guaranteeing data accuracy, which enabled the search for risk factors related to adhesiolysis injury. Previous studies had to rely on medical records, which are often inaccurate when reporting adhesive complications.(15-17) The present results were obtained using robust statistical methods and were validated internally using bootstrapping.

Although this prediction model shows a good fit, it only identifies groups with low and moderate risk of bowel injury, with predicted risks ranging between 0 and 50 per cent. The inability to predict incidences above 50 per cent is most likely due to the many operative aspects that can result in bowel injury, the absence from the present data of other potentially relevant risk factors, and unknown risk factors such as the variation among humans in the extent and severity of adhesion formation after a similar insult. It is questionable whether prediction of complications after surgery could ever reach 100 per cent considering the interaction of multiple patient, surgeon and local environmental factors. Recently a prediction model for development of surgical-site infection found an incidence ranging from 15.6 to 36.1 per cent; a model predicting the need for blood transfusion in head and neck surgery yielded rates ranging from 0.5 to 62 per cent.(18;19) The present model identified predictive factors that are easily assessed from the history of all elective surgical patients. This enables the prediction model to be validated in external populations.

In this study, previous laparoscopic surgery was not identified as a risk factor for bowel injury. This finding should be interpreted with caution because of the low incidence of major previous laparoscopic procedures in this series. There are limited data showing less adhesion formation and better adhesion-related clinical outcome with gynaecological laparoscopy and other minor general surgical procedures.(20) Evidence regarding laparoscopic colorectal surgery is not convincing, particularly because adhesion formation was assessed *post hoc* or as a secondary outcome in colorectal studies.(21;22)

Other potential preoperative factors for prediction of adhesion-related complications are the use of adhesion barriers, and mapping of adhesions to the abdominal wall and between viscera.(11) Adhesion barriers were barely used in any of the previous operations in the present cohort, consistent with the low use of barriers reported in surveys.(10;23) Adhesion mapping was not included as a variable here because such diagnostic tools are still experimental.(24-26) No routine diagnostic tool exists that can reliably assess adhesions before surgery, especially those between viscera.

Two previous retrospective studies provided evidence that the number of previous laparotomies increases the risk of bowel injury at adhesiolysis.(6;17) In these studies age was also a risk factor, which could not be confirmed in the present cohort. Other risk factors identified in the present study had either not been analysed previously or did not show a significant effect. (6;16;27)

Some variables identified as potential risk factors in univariable analysis were not significant in the final multivariable risk model, including history of peritonitis, mesh *in situ* and time since last laparotomy, which have been associated with more dense and extensive

adhesions in other studies.(7;28-31) Numbers in these subgroups might have been too small to demonstrate significance.

There was no difference in the risk of bowel injury between senior and junior consultants, and residents. However, high-risk patients were often scheduled for surgery by a consultant (or at least with a consultant available to assist), which might have obscured the impact of surgical experience in this observational study.

Although the statistical background of the risk model presented is complex, patients at risk of bowel injury are easily identified using the nomogram based on the four predictive factors from the multivariable model. Fewer than 10 per cent of surgeons inform their patients about the risks of adhesions.(10) Given the high risk of morbidity and increased perioperative mortality associated with bowel injuries, not informing patients about these risks could be deemed negligent.(32) The present results may be used to weigh up the risks and benefits of surgery for the individual patient. Most patients undergoing abdominal surgery have a vital (oncological) indication for surgery. However, many others with benign conditions undergo abdominal surgery to improve quality of life (ventral hernia with mainly cosmetic complaints). In these patients, the potential benefits of the operation and the risk of reducing quality of life owing to bowel injury can now be discussed more appropriately. Having identified a high-risk patient, precautions can be taken, such as scheduling extra operating theatre time, and recruiting a dedicated consultant and operating room team.

Future studies are needed to evaluate whether reduction of adhesion formation by the use of adhesion barriers can decrease the risk of bowel injury during reoperations.(11;33)

Acknowledgements

The authors thank P. G. Anderson for reviewing the manuscript contextually and grammatically.

Disclosure: The authors declare no conflict of interest.

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Part III: Adhesion prevention

Chapter 8: Different surgical techniques to reduce postoperative adhesion formation: a systematic review and meta-analysis

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Published in: Human Reproduction Update. 2013;19;12-25

Abstract

Introduction

Adhesion formation is the most common complication following peritoneal surgery and the leading cause of small bowel obstruction, acquired infertility and inadvertent organ injury at reoperation. Using a 'good surgical technique' is advocated as first step in preventing of adhesions. However, the evidence for different surgical techniques to reduce adhesion formation needs confirmation.

Materials and methods

Pubmed, Embase and CENTRAL were searched to identify randomized controlled trials that investigated the effect of various aspects of surgical technique on adhesion-related outcomes. Clinical outcomes and incidence of adhesions were the primary endpoints. Identification of papers and data extraction was performed by two independent researchers.

Results

28 papers from 27 studies included for a systematic review. Of these, 17 studies were eligible for meta-analysis, and 11 for qualitative assessment only. None of the techniques that were compared significantly reduced the incidence of adhesive small bowel obstruction. In a small low quality trial, the pregnancy rate increased after subserous fixation of suture knots. However, the incidence of adhesions was lower after laparoscopic compared to open surgery [relative risk (RR) 0.14; 95% confidence interval (CI): 0.03-0.61] and when the peritoneum was not closed (RR 0.36; 95% CI 0.21-0.63).

Conclusion

None of the different techniques that were compared reduced the two main adhesion-related clinical outcomes, small bowel obstruction and infertility. The meta-analysis provides little evidence to the surgical principle that less invasive techniques, introducing less foreign bodies or causing less ischemia reduces the extend and severity of adhesions.

Introduction

Post-operative adhesions form as a result of peritoneal injury in abdominal and pelvic surgery, abdominal inflammatory diseases and infection.(1-4) Adhesions may cause a wide variety of morbidities, including adhesive small bowel obstruction (ASBO), acquired female infertility, chronic abdominal pain and inadvertent organ injury during repeat surgery.(5-10) The risk for adhesion-related complication is highest following colorectal surgery and surgery of the ovaries, with a 10-year risk of readmission directly related to adhesions as high as 8.8 and 7.5%, respectively.(11-13)

Prevention of post-surgical adhesion formation is the only way to combat adhesion-related morbidity because proper medical treatment does not exist and surgical adhesiolysis has the drawback of adhesion reformation. The first step in preventing post-operative adhesions is applying a so-called ‘good surgical technique’ minimizing injury to serosal surfaces and the parietal peritoneum. The significance of minimizing peritoneal injury had been emphasized in numerous reports, however, without substantiating on what constitutes good surgical technique from a number of anti-adhesion measures and agents.

Aspects of surgical technique often mentioned in literature to be associated with (reduction of) adhesion formation are laparoscopy, closure of the parietal peritoneum, foreign bodies (e.g. glove powder, sutures and meshes), electrocautery, infection (prevention) and peritoneal lavage. Some studies show conflicting results. Recent clinical observational studies demonstrated a lower incidence of adhesions following laparoscopy in comparison with open surgery.(14-17) However, laparoscopy did not significantly reduce adhesion related morbidity in a large population-based study.(4) Animal experiments demonstrated an unfavourable effect of CO2 pneumoperitoneum at laparoscopy on peritoneal perfusion, reactive oxygen species formation and desiccation of the peritoneum, all of which are factors known to induce adhesion formation.(18) Peritoneal closure in order to reduce adhesion formation is much debated, especially following a Caesarean section.(19-21) Animal studies have demonstrated that the choice of suture material influences adhesion formation by its effect on the inflammatory response and that unipolar electrocautery causes more thermal injury to the peritoneum than ultrasonic dissection in a rat model of direct peritoneal injury.(22;23)

A recent questionnaire among Dutch surgeons indicated that many questions exist regarding the influence of surgical technique on adhesion formation and there seems to be a need for clear recommendations and guidelines in order to adhere to the best surgical technique based on the best available clinical evidence.(24)

A few randomized clinical studies have been published investigating certain aspects of surgical technique with regard to peritoneal adhesion formation. The endpoints of these studies vary from direct observation of the incidence of adhesions during second-look surgery to assessment of the fibrinolytic response to peritoneal injury as an indirect measure of adhesion formation. Although these studies indicate a pivotal role for fibrinolysis in adhesion formation, fibrinolytic activity has never been validated as a surrogate outcome for the incidence of adhesions or related morbidity.(25)

This study aimed to systematically review all randomized clinical trials (RCTs) comparing surgical techniques in patients undergoing abdominal or pelvic surgery with direct endpoints of adhesion formation to obtain evidence of good surgical techniques that reduce adhesion formation.

Materials and methods

Search

A comprehensive literature search was carried out in Pubmed, Embase and CENTRAL. A list of predefined search terms was combined with the Cochrane Highly Sensitive Strategy for Pubmed (Table 1). Similar keywords were used for searching Embase and CENTRAL. The EMBASE search was combined with the sensitivity maximizing search strategy described by Wong et al.(26) No language or date restrictions were applied. The latest search was carried out on 1 October, 2011. A manual search of the bibliographies of relevant papers was carried out to identify additional studies for possible inclusion.

Paper selection

Identified articles were screened for the following inclusion criteria in title and abstract: patients undergoing intra-peritoneal surgery; comparison of different surgical techniques; at least one of the outcome measures as defined below and randomized trials. If in doubt, full text of articles was retrieved. Multiple publications of one original RCT were excluded when the papers did not add new information for quality assessment of the predefined outcomes.

Outcomes

Primary outcomes were the incidence of ASBO, pregnancy rate and incidence of adhesions at second-look surgery.(27) ASBO was regarded as a valid outcome only if the diagnostic criteria for ASBO were clearly described. Pregnancy rate was regarded as a valid measure of clinical success only in those studies where included patients underwent gynaecologic surgery and had clear pregnancy desire. Both the total number of clinical pregnancies and live births were analysed. Secondary endpoints were the site-specific incidence of adhesions and the standardized mean difference (SMD) in adhesion score.

Data and statistical analysis

Identification of papers and extraction of data were performed by two independent researchers (R.P.G.B. and N.K.-K.) and discrepancies were resolved through discussion under supervision of a third author (H.G.). We described outcomes and risk of bias of all articles, using the Cochrane Collaboration's tool for assessing risk of bias. Studies were eligible for meta-analysis if the methods of follow-up were adequate for the outcome and necessary statistics could be retrieved. Follow-up was considered adequate if the length of follow-up was sufficient for the outcome to occur, data were obtained from a prospective source and ,20% of patients were lost to follow-up. If statistics for meta-analysis were not provided or inconsistent in the full text of articles, email contact or, if necessary, telephone contact with the primary author was made to obtain the missing data. If the author could not provide these data, the main findings were only described and the study was excluded from meta-analysis.

Table 1: Predefined search terms used in Pubmed

PATIENTS
1. abdo*[Title/Abstract]
2. intraabdominal[Title/Abstract]
3. peritoneal[Title/Abstract]
4. intraperitoneal[Title/Abstract]
5. laparoscop*[Title/Abstract]
6. laparotom*[Title/Abstract]
7. myomect*[Title/Abstract]
8. gyne*[Title/Abstract]
9. surgi*[Title/Abstract]
10. surge*[Title/Abstract]
11. leostom*[Title/Abstract]
12. colon*[Title/Abstract]
13. color*[Title/Abstract]
14. pelv*[Title/Abstract]
15. cesarean section [Title/Abstract]
16. caesarean section [Title/Abstract]
17. COMBINE 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16
INTERVENTIONS
18. electrocoag*[Title/Abstract]
19. electrotherm*[Title/Abstract]
20. ultrason*[Title/Abstract]
21. harmonic scalpel[Title/Abstract]
22. ultracision[Title/Abstract]
23. periotneal[Title/Abstract]
24. peritoneum[Title/Abstract]
25. lavage[Title/Abstract]
26. sutur*[Title/Abstract]
27. closure[Title/Abstract]
28. powder[Title/Abstract]
29. foreign*[Title/Abstract]
30. laparoscop[Title/Abstract]
31. laparotom*[Title/Abstract]
32. hydra[Title/Abstract]
33. conditioning[Title/Abstract]
34. antibio*[Title/Abstract]
35. laser[Title/Abstract]
36. COMBINE 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35
CONTROL
-
OUTCOME
37. adhesi*[Title/Abstract]
38. tissue adhesions[MeSH Terms]
39. COMBINE 37 OR 38
TOTAL
40. COMBINE 17 AND 36 AND 39

Similar keywords were used for searching Embase

Data extraction and meta-analysis were performed following the recommendations of the Cochrane Handbook and QUOROM statement. Studies designed to assess an adhesion end-point, with low risk of bias on at least three domains, ,10% of patients lost to follow-up and no important flaws in design were considered high-quality RCTs. When appropriate, a separate analysis was made for high-quality and low-quality studies in addition to the pooled analysis. The Mantel–Haenszel method was applied for pooling of dichotomous data and presented as relative risk (RR) with 95% confidence interval (CI). The inverse variance method was used for pooling continuous data and this was presented as SMD and 95% CI. A

fixed-effects model was applied for meta-analysis. In the presence of significant heterogeneity, a random effects model was applied. Heterogeneity was tested with x2 and I2 test. An I2 value ≥50% or a P-value ,0.05 was considered significant. Data were analysed using Review Manager 5.0 (The Cochrane Collaboration, Copenhagen, Denmark).

A summary of the results from the meta-analysis was presented in a figure showing the number of studies, number of participants and relative risk with 95% CIs for all primary outcomes per comparison of techniques.

Results

Description and quality of included studies

Searches identified 3912 publications. After removal of duplicates, abstracts and titles of 2854 publications were assessed. There were 59 potentially relevant papers were identified from title and abstract, and 31 papers were excluded. One paper was written in Romanian language and full text could not be retrieved. The other 30 papers were excluded from analysis after reading the full text. There were 25 papers excluded because they did not compare different surgical techniques or did not report an adhesion-related outcome. Four papers encompassed studies already included and provided no additional information on outcomes or methodology. Only one paper described a study protocol (Fig 1).

Finally, 28 papers from 27 studies were included. Two papers of Lundorf et al. reported results on different outcomes of the same trial.(28;29) The methodological quality of most studies was poor, the median number of domains with low risk of bias was 2 (range 0–5; Table 2). The low-quality resulted from inadequate description of randomization methods, lack of observer blinding and lack of power analysis. Ten studies had high rates of withdrawals and dropouts or gave no explanation for loss to followup. Eight of these had rates of patients lost to follow-up varying between 31.1 and 81.9%; five of these studies addressed Caesarean section. Two further confounders were detected that might have influenced the validity of the outcome parameters. In five studies, second look was performed by a repeat Caesarean section. This might have introduced a selection bias at the second-look operation, because patients who develop periadnexal adhesions have more difficulty conceiving a second time. Three studies with pregnancy as an outcome parameter described no or incomplete fertility assessment of patient and partner.

Of the 28 papers, 17 were included in the meta-analysis (see Table 3 for characteristics). The remaining 11 papers were excluded from meta-analysis because of inconsistency in data or inadequate follow-up. Two papers had inconsistencies in the presented data, which could not be resolved via email contact with the authors.[30;31] In two papers, the incidence of small bowel obstruction was established using retrospective data from operative notes.[32;33]. In the remaining papers more than 20% of patients did not return for the second-look operation (Table 4).

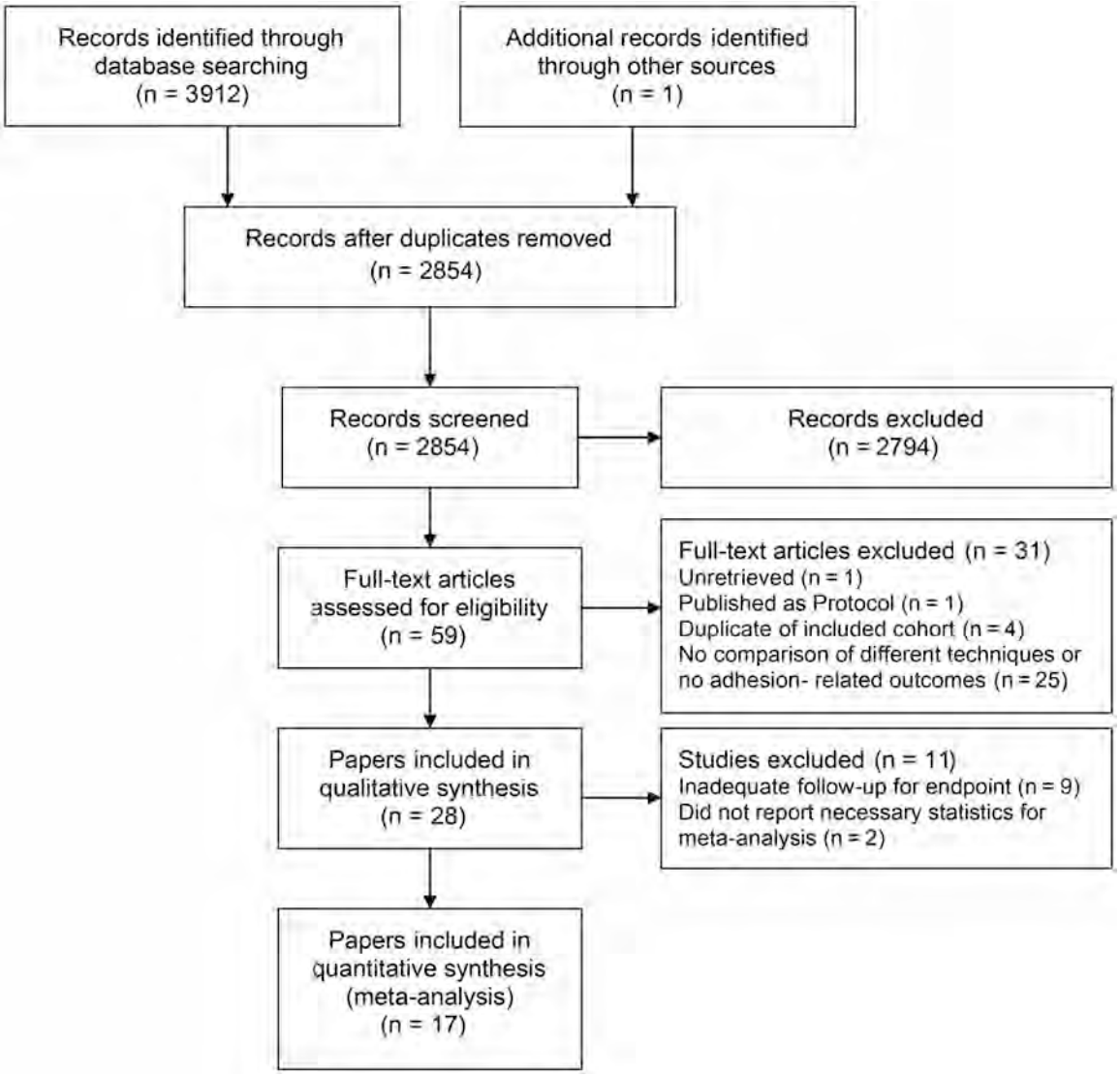

Figure 1 Quorom flow chart illustrating the selection procedure of relevant articles. RCT, randomized clinical trial

All 27 studies were published between 1986 and 2010 and addressed different topics of surgical technique. There were 23 studies performed in patients undergoing gynaecological surgery and four studies in patients undergoing general abdominal surgery. Five topics of surgical technique were studied in more than one study; closure of the parietal peritoneum (seven papers), laparoscopy or laparotomy (six papers), use of laser during surgery (two papers) and suturing following salpingotomy (two papers). Two studies in women with acquired infertility compared fertility rates after singlestage fertility surgery versus fertility surgery with a second-look laparoscopy. Other topics were the technique used for Caesarean section, the use of sutures in comparison to electrocautery to achieve haemostasis, two suturing techniques in laparoscopic myomectomy, two suturing methods following salpingotomy, the type of incision in the operative treatment of bowel perforation and a variety of techniques for laparoscopic ovarian drilling in patients with polycystic ovarian syndrome. Median sample size was 75 (range: 17–794).

Outcomes

Results from the meta-analysis are summarized in Fig 2. Results per comparison and the results from qualitative assessment of the 11 papers not suitable for meta-analysis are described in detail below.

Laparoscopy versus Laparotomy

Six papers were published comparing adhesion formation between laparoscopy and laparotomy. Four studies of patients undergoing bowel resection reported on ASBO as secondary end-point and thus were not powered for ASBO. Two trials assessing incidence of ASBO were suitable for meta-analysis.(34;35)

The incidence of ASBO confirmed by surgery was not significantly different between patients undergoing laparoscopy or laparotomy (RR 0.14; 0.02–1.12; P = 0.06).Ng et al. additionally reported the incidence of clinical suspicion of ASBO, which was lower in patients undergoing laparoscopy (RR 0.14; 95% CI: 0.03– 0.61; P = 0.008).(35)

Two trials compared pregnancy rate following laparoscopic or open surgery.(29;36) The results were highly heterogeneous (I2= 72%). Using a random effects model, there was no significant difference in clinical pregnancy rate (RR 1.28; 95% CI: 0.94–1.74; P = 0.12). There was also no significant difference in live births in one study (RR 0.88; 95% CI: 0.40–1.90).(37) Adhesions at second look were found in 1/39 patients (2.6%) after laparoscopy, compared with 30/37 patients (81.1%) after open gynaecological surgery (RR 0.03; 95% CI: 0.00–0.22;P < 0.001) in one trial.(36)

Two studies analysed the incidence of ASBO retrospectively in cohorts previously randomized between laparoscopic or open colorectal surgery. Taylor et al. found no significant difference in the incidence of ASBO between patients operated laparoscopically or by open surgery (7/280; 2.5% vs. 4/131; 3.1%; P=0.749).(33) In the study of Stocchi et al. 2/27 patients in the laparoscopic group versus 0/29 patients in the open group required reoperation for ASBO (P=0.23).(32)

The study of Lundorff et al. was excluded for meta- analysis on the outcome incidence of adhesions because 27.8% of randomized patients did not return for a second look laparoscopy.(28) In this study, the incidence of adhesions was 18/31 (58.1%) following laparoscopic and 33/42 (78.6%) following open surgery, but this difference was not significant (P=0.08).

Peritoneal closure

Seven of the included studies compared adhesion formation after peritoneal closure or non-closure of the peritoneum. Three trials were eligible for meta-analysis.(21;38;39) One high-quality trial studied the incidence of ASBO following hysterectomy and pelvic node dissection in 120 patients. Only one patient in the non-closure group was reoperated for ASBO, with the adhesive band found at the plane of the pelvic node dissection. The difference was not significant (2.95; 95% CI:0.12–73.9; P = 0.51).(38) The incidence of adhesions was significantly lower when the peritoneum was left open in one trial (RR 0.36; 95% CI: 0.21–0.63; P < 0.001).(39) The adhesion score was significantly lower in a high-quality trial in patients with ovarian cancer, when the peritoneum was not closed 9.1+2.8 versus 6.1+2.4; SMD -1.14 (95% CI: -1.56, -0.72; P < 0.001).(21)

Table 2 Risk of bias assessment summary

Reference	Adequate sequence generation	Allocation concealment	Blinding (observer)	Adequate Reporting on loss to follow-up	Power analysis	Free of other sources of bias	Domains with low risk of bias (N)	Comment – other source of bias
Alborzi (2003)	YES	NR	NO	NO	NR	NO	1	Adhesion score used is highly subjective
Eshuis (2010)†	YES	YES	NO	NO	YES	YES	4	
Fujishita (2004)	YES	NR	NO	NO	NR	NO	1	Not all randomized patients had pregnancy desire; No fertility analysis described
Franchi (1997)	YES	NR	NR	YES	YES	YES	4	
Gurgan (1991)	NR	NR	NR	NR	NR	NR	0	Randomization of patients not explicitly reported
Gurgan (1992)	YES	NR	NO	YES	NR	NR	2	No assessment and comparison of adhesion in initial surgery
Kadanali (1996)	NR	YES	YES	YES	NR	NR	3	Length till second look operation not described
Kapustian (2011)	YES	NR	YES	NO	YES	NO	3	Repeat caesarean section might introduce selection bias
Komoto (2006)	NO	NO	NO	NO	NR	NO	0	Repeat caesarean section might introduce selection bias
Lundorff (1991 - 1993)	YES	YES	NO	NO	NR	NO	2	Second look not planned for all randomized patients; Not all randomized patients had pregnancy desire
Malvasi (2009)	NO	NO	NO	YES	NR	NR	1	Repeat caesarean section might introduce selection bias
Mercorio (2008)	YES	YES	NO	YES	NR	YES	4	
Nabhan (2008)	YES	YES	NO	NO	YES	NO	3	Repeat caesarean section might introduce selection bias
Ng (2009) [a]	YES	YES	NO	YES	YES	YES	5	
Pellicano (2005)	NO	NR	NO	YES	NR	NO	1	No fertility analysis described
Pellicano (2008)	YES	NR	YES	YES	NR	NO	3	Problems with statistical analysis
Roy (2009)	NR	NR	NR	YES	NR	NO	1	Second look only in patients who failed to conceive, excluded for outcome second look
Sharma (2006)	YES	NR	NR	YES	NR	NO	2	Fertility analysis described is incomplete; Pregnancy rate in abstract does not correspond to rate in full text.
Stocchi (2008)	NR	NR	NR	YES	NR	NO	1	No prospective follow-up; might have included some patient before start of randomization
Takahashi (2007)	NR	NR	NO	YES	NR	YES	2	Randomization of patients not explicitly reported
Talwar (1997)	NO	NO	NO	NR	NR	NO	0	Criteria for clinical diagnosis of ASBO not given
Taskin (1999)	YES	NR	NR	NR	NR	NO	1	Inconsistencies in reported outcomes
Taylor (2010)	YES	YES	NR	NO	YES	NO	3	No prospective follow-up
Tulandi (1986)	NR	NR	NR	NR	NR	NR	0	Overall methodology poorly described
Tulandi (1991)	NR	NR	NR	NR	NR	NR	0	Inconsistencies in reported outcomes
Weerawetwat (2004)	NR	NR	YES	NO	NR	NO	1	Repeat caesarean section might introduce selection bias
Zareian (2006)	YES	YES	NR	NO	NR	NO	2	Repeat caesarean section might introduce selection bias

ASBO, adhesive small bowel obstruction.

[a]Primary powered outcome not adhesion related. NR; not reported or report insufficient for judgement.

Table 3 Characteristics of trials included in meta-analysis

Study	Period	Patients	Interventions	n	Outcomes	Lost to follow- up per outcome	Follow up in months
Laparoscopy vs. Laparotomy							
Eshuis (2010)	1999 – 2003	Ileocolic resection for Chrohns disease	Laparoscopy Laparotomy	30 30	ASBO - reoperation	5/ 60 (8.3%)	68 - 95
Ng (2009)	1993 – 2002	Anterior resection for upper rectal cancer	Laparoscopy Laparotomy	76 77	ASBO - reoperation ASBO - clinical	5/ 153 (3.3%) 5/ 153 (3.3%)	71 - 168
Lundorff (1991-1993)	1987 - 1989	Patients with ectopic pregnancy.	Laparoscopy Laparotomy	48 57	Pregnancy	18/ 105 (17.1%)	1 - 36
Takahashi (2007)	NR	Polycystic ovarian syndrome	Laparoscopy Laparotomy	39 37	Second look Pregnancy	0/ 76 (0%) 0/ 76 (0%)	1 week 12
Peritoneal Closure vs. No Peritoneal Closure							
Kadanali (1996)	1992 – 1995	Lymphadenectomy in ovarian cancer	Peritoneal closure No peritoneal closure	50 52	Second look	0/ 102 (0%)	NR
Franchi (1997)	1991 – 1995	Hysterectomy and pelvic node dissection	Peritoneal closure No peritoneal closure	59 61	ASBO – reoperation	0/120 (0%)	11 – 72
Malvasi (2009)	2003 – 2007	Caesarean section	Peritoneal closure No peritoneal closure	54 58	Second Look	0/ 112 (0%)	NR
Hemostasis							
Laser vs. Electrocautery							
Gürgan (1991)	NR	Poly Cystic ovarian syndrome	Laser Electrocautery (unipolar)	10 7	Second Look Pregnancy	0/ 17 (0%) 0/ 17 (0%)	3 – 4weeks 6
Tulandi (1986)	NR	Periadnexal adhesions	Laser Electrocautery (unipolar)	30 33	Pregnancy	0/ 63 (0%)	NR
Sutures vs. Electrocautery							
Pellicano (2008)	2004 – 2005	Ovarian endometrioma	Suturing Electrocautery (bipolar)	16 16	Second Look	5/ 32 (15.6%)	60- 90 days
Second Look Surgery vs. No Second Look Surgery							
Alborzi (2003)	NR	Adnexal adhesions	Second look No second look	46 44	Pregnancy	0/ 90 (0%)	12
Gürgan (1992)	NR	Poly Cystic ovarian syndrome	Second look No second look	19 20	Pregnancy	0/ 39 (0%)	6
Various Techniques in Laparoscopic Surgery for Polycystic Ovarian Syndrome							
Sharma (2006)	NR	Poly Cystic ovarian syndrome	Unipolar electrocautery Bipolar electrocautery	10 10	Pregnancy	0 / 20 (0%)	NR
Mercorio (2008)	2002 – 2006	Poly Cystic ovarian syndrome	12 punctures 6 punctures	96[a] 96[a]	Second Look	12 /182* (6,3%)	4 – 9 weeks
Roy (2009)	2005 – 2007	Poly Cystic ovarian syndrome	Bilateral Unilateral	22 22	Pregnancy	0 / 44	12
Miscellaneous							
Pellicano (2005)	2001 – 2002	Laparoscopic myomectomy	Subserous sutures Figure- eigth sutures	18 18	Pregnancy	0 / 36	12
Talwar (1997)	1994 – 1996	Typhoid enteric perforation- type of incision	Rutherford- Morrison Right paramedian	27 29	ASBO	0 / 56	4 – 12

NR; not reported.

[a] Randomization unit is ovary.

Table 4 Characteristics of studies included in qualitative assessment.

Study	Period	Patients	Interventions	n	Outcomes	Lost to follow- up per outcome	Follow up in months
Laparoscopy vs. Laparotomy							
Lundorff (1991-1993)	1987 - 1989	Patients with ectopic pregnancy.	Laparoscopy Laparotomy	48 57	Second look Pregnancy	32/ 105 (27.8%) 18/ 105 (17.1%)	12 weeks 1 - 36
Stocchi (2008)	NR	Ileocolic resection for Chrohns disease	Laparoscopy Laparotomy	27 29	ASBO - reoperation	0/27 (0%) 0/29 (0%)	120 ± 38[a] 132 ± 17[a]
Taylor (2010)	1996 – 2002	Colorectal cancer	Laparoscopy Laparotomy	526 268	ASBO - reoperation	246/ 526 (46.8%) 131/ 268 (48.9%)	36
Peritoneal Closure vs. No Peritoneal Closure							
Kapustian (2011)	2004 – 2007	Caesarean section	Peritoneal closure No peritoneal closure	47 50	Second look	436/533 (81.8%)	NR
Komoto (2006)	1995 – 2000	Caesarean section	Peritoneal closure No peritoneal closure	70 54	Second look	74/ 124 (59.7%)	NR
Weerawetwat (2004)	1987 – 1991	Caesarean section	Peritoneal closure No peritoneal closure	240 120	Second Look	295/ 360 (81.9%)	NR
Zareian (2006)	1999 – 2004	Caesarean section	Peritoneal closure No peritoneal closure	24 21	Second Look	14/ 45 (31.1%)	NR
Techniques in Cesarean Section							
Nabhan (2008)	2002 – 2007	Caesarean section	Pfannenstiel – Kerr Joel – Cohen – Stark	300 300	Second Look	476/ 600 (79.3%)	NR
Suturing vs. No Suturing Following Salpingotomy							
Fujishita (2004)	1996 – 2002	Salpingotomy for ectopic pregnancy	Sutures No sutures	32 43	Pregnancy	43/ 75 (57.3%)	6 – 65
Tulandi (1991)	NR	Salpingotomy for ectopic pregnancy	Sutures No sutures	19 15	Second Look	8/ 19 (42.1%) 8/ 15 (53.3%)	24
Taskin (1999)	NR	Poly Cystic ovarian syndrome	Microlaparoscopy Laparoscopy	9 9	Second Look	?/ 9 ?/ 9	2- 3 weeks
Miscellaneous							
Pellicano (2005)	2001 – 2002	Laparoscopic myomectomy	Subserous sutures Figure- eigth sutures	18 18	Pregnancy	0 / 36	12
Talwar (1997)	1994 – 1996	Typhoid enteric perforation- type of incision	Rutherford- Morrison Right paramedian	27 29	ASBO	0 / 56	4 – 12

NR; not reported
[a] Mean ± SD

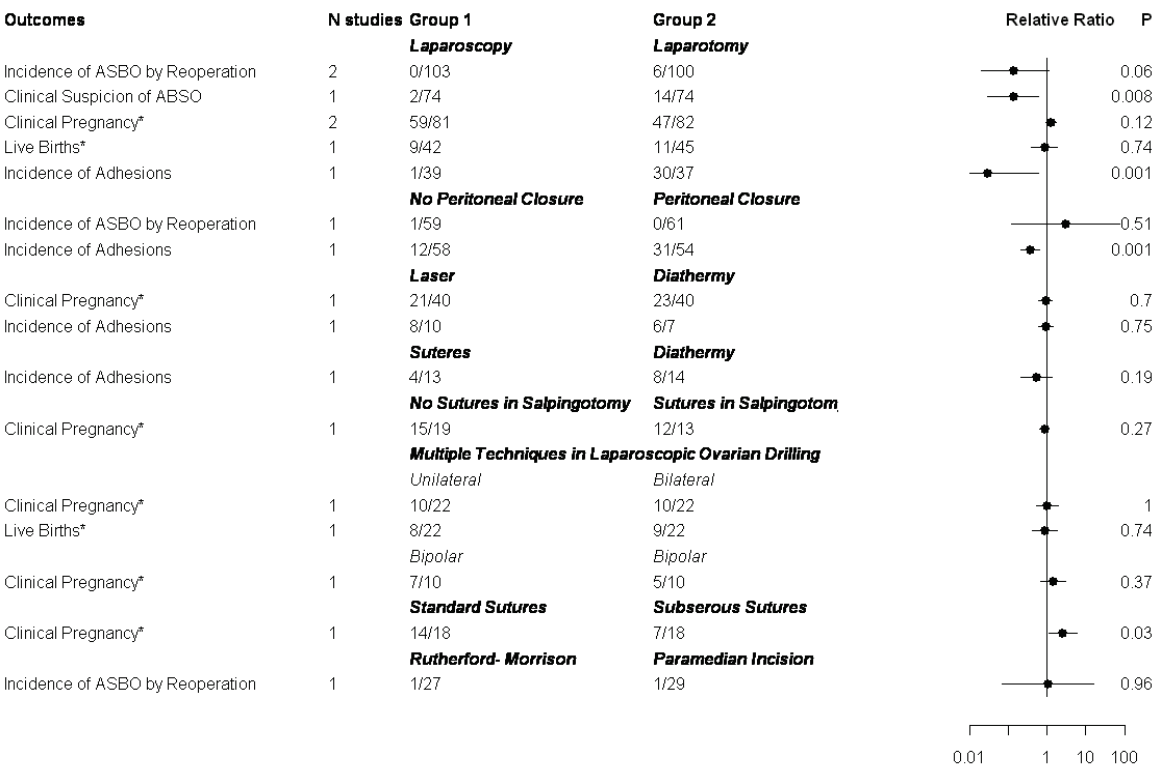

Figure 2 Summary of meta-analysis presenting relative ratio with CI for primary outcomes per comparison of techniques.

Four studies investigating adhesion formation after closure or nonclosure of the peritoneum in Caesarean section were excluded from meta-analysis because only a small portion of patients returned for a second operation with evaluation of adhesion formation.(40-43) The results from these studies were highly heterogeneous (I2= 67%) and a mean of 77.1% of patients were lost to follow-up. No conclusions could be drawn from these studies on the incidence of adhesions after closure or non-closure of the peritoneum (RR 1.02; 95% CI: 0.43–2.40; P = 0.97).

Two Techniques of Caesarean Section

The study of Nabhan et al. on Caesarean section was separately analyzed because operative technique between the experimental and control group differed on more aspects than peritoneal closure alone. This study was not suitable for meta-analysis because 79.3% of patients was lost to follow-up.(44) In the standard technique control group, Caesarean section was performed using the traditional Pfannenstiel-Kerr technique, making a bladder flap and closing the peritoneum. In the modified technique group, the Joel-Cohen-Stark technique (based on the Misgav Ladach technique) was used, without making a bladder flap and without closing the peritoneum. The incidence of adhesion was significantly lower in the modified technique group (11.3% vs. 35.5%; P=0.003).(44) Obviously, this reduction cannot solely be attributed to peritoneal non-closure.

Hemostasis

Two trials compared pregnancy rate between patients treated with laser and patients treated with unipolar electrocautery.(45;46) Gürgan et al. randomized between electrocautery and ND:YAG laser in 17 patients and Tulandi et al. randomized 63 patients between CO_2- laser and electrocautery. There were no differences in pregnancy rate using laser devices compared with electrocautery (RR 0.93; 95% CI: 0.62- 2.21.371; P=0.70). No information could be obtained on the number of live births following conception. All patients who conceived in the trial of Gürgan et al. had intrauterine pregnancies.(45) Three of the pregnancies in the trial of Tulandi et al. were ectopic, two in the electrocautery group and one in the laser group; this difference was not significant.(46) Gürgan et al. additionally found no difference in incidence of adhesions during a second look laparoscopy (RR 0.93; 95% CI: 0.62 – 1.44; P=0.75).(45)

Pellicano et al. randomized 32 women undergoing surgery for ovarian endometrioma.(47) Haemostasis was achieved by intra-ovarian suturing with only light additional coagulation if necessary or by using bipolar coagulation only. The adhesion score, expressed by the American Society for Reproductive Medicine score, was significantly lower in the suturing group at a second look, 5.4 ± 2.1 versus 10.3± 2.9 (SMD-1.87; 95% CI: -2.79, -0.94; P<.001). Incidence of adhesions was not significantly different (RR 0.54; 95% CI: 0.21-1.37; P=0.19).(47)

Second look fertility surgery

Two trials in fertility surgery compared pregnancy rates between patient undergoing single-stage fertility surgery and patients who had second-look laparoscopy.(48;49) There were 129 patients randomized and there was no loss to follow-up. The pregnancy rate was 22/65 (33.8%) in patient with second-look surgery compared to 30/64 (46.9%) after single-stage surgery (RR 0.73; 95% CI: 0.48- 1.11; P=0.14). In the trial of Alborzi et al. the number of live births was 11/46 (23.9%) in the second-look group, compared with 15/44 (34.1%) in the single-stage surgery group (RR 0.55; 95% CI: 0.30- 1.03; P=0.06).(49)

Suturing in Salpingotomy

Two studies analysing pregnancy rates after suturing or no suturing following salpingotomy were included in the qualitative assessment. Fujishita et al. analysed the pregnancy rate in 32 patients with a pregnancy desire. In the group without suturing, 15/19 (78.9%) conceived, compared with 12/13 (92.3%) in the group with suturing after the salpingotomy. The difference was not significant (P=0.27).(50) The number of live births was not reported.

Tulandi et al. reported the intrauterine pregnancy rate after randomizing 34 patients to salpingotomy with or without suturing. The reported 2-year pregnancy rate was 45% in the nonsuturing group and 47% in the suturing group.(30)

Laparoscopic ovarian drilling

Three trials addressed distinct aspects of laparoscopic ovarian drilling in patients with polycystic ovarian syndrome. The clinical pregnancy rate was comparable in one study randomizing 44 patients between unilateral compared and bilateral treatment (RR 1.00; 0.52, 1.91; P=1.00), in both groups 10/22 patients became pregnant. The number of live births was 8/22 in the unilateral group and 9/22 in the bilateral group (RR 0.89; 95% CI: 0.42-1.88; P=0.74).(51) Sharma et al. studied the pregnancy rate following laparoscopic ovarian drilling after randomizing between bipolar or unipolar electrocautery in 20 patients. In the bipolar group 7/10 (70%) patients conceived, compared with 5/10(50%) in the unipolar group (RR

1.40; 95% CI: 0.67, 2.94; P=0.37). The number of live births was four in the unipolar group and was not reported for the bipolar group, thus comparison was not possible.(52) Mercorio et al. randomized the right and left ovary to 6 or 12 puncture holes in 90 women undergoing bilateral ovarian drilling using a unipolar electrocautery technique. The site specific incidence of adhesions was 41/90 or 42/90, respectively, after 6 or 12 punctures (RR 0.98; 95% CI: 0.71- 1.34; P= 0.88).(53)

Miscellaneous

Pellicano et al. compared two techniques of suturing in patient undergoing laparoscopic myomectomy. Subserous suturing was done with a first deep uterine crossing of the suture and a second subserous transfixation of the knot. This was compared with deep figure of eight suturing as the standard treatment.(54) Both suturing methods where tested among two groups, one with and one without additional use of an anti-adhesive hyaluronic acid gel. A trend towards a higher pregnancy rate was demonstrated for the subserous sutures in both the anti-adhesive gel group and the group without adhesion barrier. Clinical pregnancy rate was significantly higher when comparing subserous sutures (14/18; 77.8%) to standard sutures (7/18; 38.9%) when analysing the adhesion barrier and non-barrier groups together (RR 2.56; 95% CI: 1.11, 5.87; P = 0.03). The number of live births was not reported.

Talwar et al. analysed the incidence of ASBO in 56 patients with small bowel perforation in enteric fever, comparing a right paramedian incision to a Rutherford–Morrison incision.(55) The Rutherford– Morrison incision is a right iliac incision similar to the muscle splitting incision used for appendectomy except that all muscle fibres are cut in the same line. In both groups, one patient required reoperation for ASBO (RR 1.07; 95% CI: 0.7–16.33; P = 0.96). Clinically suspected ASBO could not be analysed because the methods of follow-up and criteria for clinical diagnosis of ASBO were not reported.

Discussion

Summary of evidence

Surgical techniques aiming to reduce adhesion formation included a large variety of technical aspects. None of the different techniques or approaches evidently showed a reduction of the main adhesion-related complications ASBO and infertility. The incidence of ASBO, established by reoperation, was not significantly different in any comparison. The clinical suspicion of ASBO was lower following laparoscopy compared with open surgery in one study. The incidence of adhesions was lower following laparoscopy than laparotomy and when the peritoneum was left open compared with peritoneal closure. However, the evidence for a lower incidence of adhesions was limited to a single small RCT and conflicting results were found in the qualitative assessment of lower quality studies. The pregnancy rate was significantly higher in one study after subserous fixation of sutures compared with standard sutures in a small low-quality RCT.

Strengths and limitations of the review

The present study is the first systematic review and meta-analysis of the impact of different surgical techniques on adhesion formation. The available evidence is predominantly from surgery of gynaecologic origin, particularly fertility surgery.(56;57) This type of surgery is often chosen in adhesion prevention research, because of the historical awareness of the adhesion problem within the European and the American fertility societies, and because the

surgery includes a second-look procedure and prevention of local adhesion (re)formation corresponds with clinical success.(58-61)

The failure to demonstrate an effect on a relevant clinical end-point such as ASBO and pregnancy in this meta-analysis has several causes. Most studies were designed to detect a difference in adhesion incidence or score. Studies with an end-point ASBO or pregnancy included a too small numbers of patients to draw meaningful conclusions. Particularly in gynaecological studies, a substantial portion of patients were lost to follow-up decreasing the number of evaluable patients. The feasibility of showing a difference in ASBO and pregnancy rates in adhesions prevention studies is a subject of debate because of the multifactorial genesis of these end-points.(27) There is a doubt about the possibility, even in studies investigating anti-adhesive agents, of including sufficient numbers of patients in a short period of time and with long enough follow-up to show a significant effect on these clinical end-points. Taking into account the small contribution of some technical aspects to the total adhesion formation following intraperitoneal surgery, it is not expected that one element of surgery will influence the incidence of ASBO and pregnancy rates. One single adhesive band may still cause a bowel obstruction.

There is some evidence from adhesion barrier studies, that reducing the incidence of adhesions results in a lower incidence of adhesion- related complications.(62;63) The outcome extent and severity of adhesions is more difficult to interpret because, unlike a reduction of incidence, reduction of extent and severity does not eliminate the risk of adhesion-related infertility or ASBO. However, patients undergoing repeated abdominal surgery might benefit from a reduction of extent and severity. High tenacity is traditionally recognized as a risk factor for organ damage during adhesiolysis.(64) In a recent prospective cohort of ventral hernia repairs, adhesiolysis time as an indicator of adhesion extent and tenacity was a strong predictor for the risk of enterotomy and complex adhesiolysis had a significant effect on morbidity and medication costs.(65) Unpublished data from a large RCT revealed that every 30 minutes of adhesiolysis was correlated to an increase in hospital stay with one day.(62) Thus, although considered secondary end-points in this review, the reduction of extent and tenacity of adhesions can be of importance especially in repeated abdominal surgery.

A large number of studies had difficulty in achieving a complete follow-up. As many as nine studies were excluded from meta-analysis because of an inadequate follow-up. Especially, the repeat Caesarean section model seems prone to high numbers of patients lost to follow-up.[40-44]. Further, the choice of a repeat Caesarean section as a second-look procedure to study peritoneal closure bears the risk of selection bias towards patients with fewer adhesions because they have a higher chance of becoming pregnant again. Such study design also leads to a large variation in follow-up period, as the timing of a next pregnancy and the need for another Caesarean section are unpredictable.

Two trials reported inconsistent statistics. These were conducted many years ago and an attempt to obtain raw data by email and telephone contacts unfortunately failed .(30;31)

Comparison with previous research

The reduction in adhesion extent and severity by limited electrocoagulation, subserous suture fixation and non- closure of the peritoneum emphasizes the importance of limiting peritoneal ischemia and foreign body material in surgery.(21;47;66) These findings concord

with histology results of peritoneal biopsies showing foreign body and ischemia induce adhesion formation in animal and human studies.(67-69) We recently demonstrated a larger peritoneal ischemic response following electrocautery in comparison to ultrasonic dissection, illustrating the adhesiogenic potential of heat application.(23) Taking down adhesions using electrocautery caused more bowel injury than with the harmonic scalpel in humans.(10)

Non- closure of the peritoneum reduced adhesion formation in this meta-analysis confirming consistent findings of animal experiments.(70-72) In the qualitative assessment of lower quality studies, adhesion reduction was not evident when the peritoneal layer was not sutured separately.(40-43;70;71) The substantial loss of follow-up, the significant heterogeneity and the predominance of repeat Caesarean sections in the low quality studies, may have contributed to the discrepancies in study outcomes.

Traditionally, closure of the peritoneum has been considered the technique of choice to reduce short-term complications and to minimize adhesion formation.(73) Contrastingly, current guidelines suggest that non-closure might be more favourable in terms of short-term complications, recovery and adhesion formation.(74;75) A Cochrane review studying short-term complications and recovery after Caesarean section found no difference between closure and non- closure of the peritoneum.(76) A recent large RCT of Caesarean sections also demonstrated no difference in short-term complications. Long-term follow-up results are still awaited.(77;78) Six RCTs addressing peritoneal closure in general surgery and following hysterectomy have demonstrated a similar incidence of incisional hernia after closure or non-closure of the peritoneum.(79-84) Summarizing the results of suturing or not suturing the peritoneum in Caesarean section, both techniques seem acceptable considering short-term complications but non-closure might decrease incidence of adhesions.

Laparoscopy was found to be favourable in randomized trials on the outcomes, incidence of adhesions and pregnancy rate. However, the studies in the qualitative assessment showed conflicting results.(28;29;36) In a large pivotal demographic study, laparoscopy failed to demonstrate a beneficial effect on morbidity related to adhesions in gynaecological patients.(4) Also no beneficial effect was found in a 3-year follow-up study in patients who were randomized to laparoscopic or open colorectal surgery.(33) In contrast, most animal data show a decrease in adhesion formation after laparoscopic compared with open surgery and observational human studies also demonstrate lower adhesiogenicity following laparoscopy.(14-17,85-88) The question is why are adhesions not more effectively prevented despite the strong concept of minimal invasive surgery inducing less tissue damage and thus a lower risk of adhesion formation. A number of factors might explain the lack of difference between laparoscopic and open surgery. First, an abdominal incision is often needed after a laparoscopic procedure to extract the specimen by an open approach. Secondly, the extent of serosal wound surfaces is comparable between open and laparoscopic procedures. Thirdly, the CO2 pneumoperitoneum, the higher intra-abdominal pressure and the light of the laparoscope being associated with peritoneal ischaemia, decreased fibrinolysis and increased adhesion formation.(18;89) Fourth, the pneumoperitoneum potentially injures the whole peritoneal surface inducing adhesion formation at remote areas. More meticulous dissection and haemostasis, no retraction of the abdominal wall and no use of gauzes in the peritoneal cavity in laparoscopic surgery counterbalance the drawbacks mentioned. The net effect on adhesion

formation and related morbidity is unknown and may only become apparent from a well-designed prospective RCT with adhesion formation as a primary outcome.

Implications for future research

The poor quality of RCT's and the limited number of eligible patients illustrate the main difficulty in clinical adhesion research, e.g. the execution of a planned second-look operation, which is the gold standard for assessment of the incidence and severity of adhesions. The number of planned second procedures has declined over recent years in both female patients who undergo planned second-look laparoscopy following fertility surgery and patients who are scheduled for a two-stage colorectal surgery with planned enterostomy take down. Second-look laparoscopy itself has no beneficial effect on fertility outcome, as confirmed in this meta-analysis, and in vitro fertilization is more widely available as an alternative treatment.(48;49;90) Improved medical treatment for Crohns disease and ulcerative colitis has significantly reduced the number of surgeries and thereby the number of planned enterostomy take downs during which adhesions can be scored.(91)

The declining number of planned second procedures is a challenge for future research in adhesion prevention. Visceral slide and cine-MRI are non-invasive adhesion detection techniques that have the potential to replace a second-look operation.(92) Cine-MRI especially holds promise identifying both adhesions to the abdominal wall and between abdominal viscera.(93;94)

Implications for clinical practice

None of the different techniques had a major impact on adhesionrelated complications. This meta-analysis provides little evidence that less invasive techniques, less foreign body material and less ischaemic injury reduce the extent and severity of adhesions in humans. The total prevention of adhesion formation is the only means to prevent an adhesion-related complication. It is not expected that optimal surgical technique alone will achieve this goal, based on the inevitable peritoneal injury inflicted by any type of surgery. As a consequence, there continues to be a need for anti-adhesion barriers and agents in open and laparoscopic surgery.[56;62;95;96]

Acknowledgements

The authors thank GJ van der Wilt, MD, PhD, professor in Epidemiology and MTA for his advice in the study design and analysis.

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Part III: Adhesion prevention

Chapter 9: Electrocautery causes more ischemic peritoneal tissue damage than ultrasonic dissection

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Published in: Surgical Endoscopy 2011; 25: 1827-34

Abstract

Background

Minimizing peritoneal tissue injury during abdominal surgery has the benefit of reducing postoperative inflammatory response, pain, and adhesion formation. Ultrasonic dissection seems to reduce tissue damage. This study aimed to compare electrocautery and ultrasonic dissection in terms of peritoneal tissue ischemia measured by microdialysis.

Methods

In this study, 18 Wistar rats underwent a median laparotomy and had a peritoneal microdialysis catheter implanted in the left lateral sidewall. The animals were randomly assigned to receive two standard peritoneal incisions parallel to the catheter by either ultrasonic dissection or electrocautery. After the operation, samples of microdialysis dialysate were taken every 2 h until 72 h postoperatively for measurements of pyruvate, lactate, glucose, and glycerol, and ratios were calculated.

Results

The mean lactate–pyruvate ratio (LPR), lactate–glucose ratio (LGR), and glycerol concentration were significantly higher in the electrocautery group than in the ultrasonic dissection group until respectively 34, 48, and 48 h after surgery. The mean areas under the curve (AUC) of LPR, LGR, and glycerol concentration also were higher in the electrocautery group than in the ultrasonic dissection group (4,387 vs. 1,639, P = 0.011; 59 vs. 21, P = 0.008; 7,438 vs. 4,169, P = 0.008, respectively).

Conclusion

Electrosurgery causes more ischemic peritoneal tissue damage than ultrasonic dissection.

Introduction

Peritoneal tissue ischemia resulting from dissection, electrocautery, sutures, carbon dioxide (CO2) insufflation (in laparoscopy), and retraction by instruments seems unavoidable in abdominal surgery. Ischemia induces an inflammatory response of the peritoneum, which is associated with postoperative pain, abdominal distension, and adhesion formation (1).

A good surgical technique is advocated to minimize tissue damage and peritoneal ischemia. The type of dissection device used during surgery may have an impact on the degree of ischemic damage. Recent reports suggest that ultrasonic dissection is superior to electrocautery (e.g., causing less deep tissue injury and less profound ischemia). The data in these reports are derived predominantly from vascular and thoracic surgery studies showing less endothelial injury and vasospasm (2; 3). Despite the wide usage of electrocautery and ultrasonic dissection in laparoscopic and open abdominal surgery, little is known about their impact on peritoneal ischemia or about related early and long-term postoperative outcomes (4).

Microdialysis is capable of continuously monitoring extracellular space chemistry, avoiding serial tissue sampling. In the past, it was predominantly used in neurointensive care monitoring of cerebral ischemia and in metabolic control. Currently, microdialysis is more widely applied to include early detection of visceral ischemia after abdominal surgery (5). It proves to be a simple and reliable technique for continuous monitoring of tissue responses to injury.

The current study aimed to assess the extent of ischemic peritoneal damage as determined by microdialysis in animals undergoing surgery with either electrocautery or ultrasonic dissection.

Materials and Methods

Animals

This study used 18 male Wistar rats weighing 250 to 300 g (Harlan BV, Horst, The Netherlands). The animals were acclimated to laboratory conditions with day–night cycles of 12 h for 1 week before commencement of experiments. The rats were housed under standard conditions in filter-topped cages, 2 rats per cage before surgery and 1 rat per cage after surgery, with free access to animal chow (Hope Farms, Woerden, The Netherlands) and water.

The study was approved by and conducted in accordance with the guidelines of the Animal Ethics Review Committee of the Faculty of Medicine, Radboud University Nijmegen, The Netherlands.

Study Design

The 18 rats were randomly assigned to a group undergoing either peritoneal tissue incision with ultrasonic dissection (UD group, n = 9) or electrocautery (EC group, n = 9). Peritoneal microdialysis was performed for 72 h after surgery, and 2-h samples were obtained to determine metabolic and ischemic parameters. The rats were killed 3 days after surgery to check the position of the catheters.

Surgical Procedure

The animals were fasted overnight and anesthetized using isofluorane, nitrous oxide, and oxygen. Procedures were performed under sterile conditions. After shaving and disinfection

with 70% ethanol, the rats underwent a median laparotomy incision with a total length of 4 cm (Fig 1A). A microdialysis catheter was implanted in the left lateral parietal peritoneum between the peritoneum and the abdominal muscle and fixed with nonresorbable 5/0 polypropylene. The connecting tubes were tunnelled subcutaneously to the top of the animal's head.

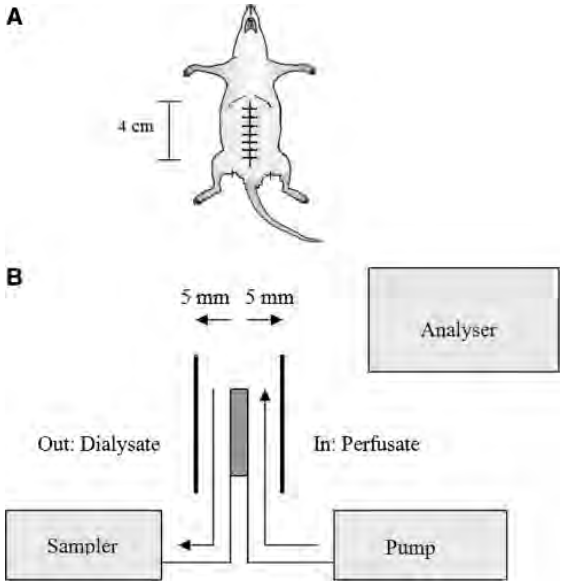

Figure 1 Surgical procedure and microdialysis system **A** Median laparotomy. **B** Two parallel incisions in the parietal peritoneum on both sides of the microdialysis catheter at a distance of 5 mm from the probe. The catheter is connected to a pump and automatic sampler.

Two parallel incisions in the parietal peritoneum with a length of 2 cm were made, both 5 mm from the catheter. (Fig 1B) The incisions were made using an ultrasonic "coagulation" blade (Harmonic Scalpel; Johnson and Johnson, Amersfoort, the Netherlands) in the UD group and using an electrocautery blade (Valleylab, Boulder, CO, USA) in the EC group. The ultrasonic coagulation was fixed at level 3 (the coagulation level normally used in humans). In the EC group, the lesions were made with a fixed rate of energy (blend 1/30 W). The contact time with the tissue was exactly 3 s for both methods of injury. The abdominal wall was closed with 3/0 polyglactin and the skin with agraves.

At the end of surgery, all the animals received buprenorphine hydrochloride 0.1 mg/kg intramuscularly and 10 ml of 0.9% NaCl subcutaneously. The animals were killed 3 days after surgery by O2/CO2 asphyxiation. The abdomen was reopened, and the catheter was inspected for location and removed.

Microdialysis

The ClinicalMicrodialysisAnalyzer/20 (CMA microdialysis, Stockholm, Sweden) was used for microdialysis. The CMA/20 microdialysis probe had a concentric construction of a soft flexible inner and outer plastic tube covered at the tip by a membrane. The probe had an outer diameter of 0.5 mm and was fitted with 200-mm-long inlet and outlet tubings. The membrane had a length of 10 mm and a cutoff of 100,000 daltons. The maximal flow rate was 10 µl/min.

After the microdialysis catheter had been inserted into the tissue, it was connected to a microdialysis pump (CMA 102; CMA, Stockholm, Sweden) and perfused at a flow rate of 0.3

μl/min. The perfusate consisted of a buffer solution (NaCl 147 mmol/l, KCl 2.8 mmol/l, CaCl2 3.4 mmol/l, K2HPO4 0.6 mmol/l, MgCl2 1.2 mmol/l, ascorbate adjusted to pH 6.9) and 40 mg/ml of Dextran 70 (Amersham Pharmacia Biotech AB, Uppsala, Sweden) administered with a 2.5-ml glass syringe (CMA, Stockholm, Sweden).

Sampling and biochemical analysis

The first sample was collected 2 h after laparotomy by a synchronized sampler (CMA/140, CMA microdialysis; CMA, Stockholm, Sweden), and automatic sampling was continued every 2 h for a total duration of 3 days. The samples were stored at –20°C.

The concentrations of peritoneal extracellular pyruvate, lactate, glucose, and glycerol were measured immediately after the whole experiment using ordinary enzymatic methods with a microdialysis-analyzer (CMA 600; CMA).

Statistical analysis

Lactate–pyruvate and lactate–glucose ratios were calculated. Data of continuous variables are expressed as means and 95% confidence intervals (CI). A two-sided t-test was calculated to evaluate any differences between two categorical variables. The area under the curve (AUC) was calculated by GraphPad, and data are expressed as mean and range. The Wilcoxon test was performed to evaluate any differences between continuous variables at different intervals. Statistical analysis was performed using SPSS 14.0 (SPSS, Chicago, IL) and GraphPad (GraphPad Prism 4.00; GraphPad Software, San Diego, CA). A P value less than 0.05 was considered significant.

Results

All the animals survived the experimental period, and a 100% sampling was obtained. All the catheters remained in position during the study period.

The unrefined data of the separate animals showed the same tendency over time within one treatment group (Fig 2). The means and 95% confidence intervals of metabolite concentrations at the time points are shown in Figure 3. Figure 3 shows the AUC, which represents the total concentration of variables in the 72-h period.

Glucose

The immediate postoperative mean glucose concentration was significantly lower in the EC group (4.7 mmol/l) than in the UD group (5.4 mmol/l; $P < 0.01$). In the animals treated with electrocautery, the mean glucose concentration decreased in the first 12 h, reaching the lowest value of 3.0 mmol/l, then increased again. The UD group showed an almost straight curve, with values of 4.9 to 5.7 mmol/l.

The mean values in the EC group were significantly lower than in the UD group for the first 36 h after surgery. The total glucose concentration, represented by the AUC, was lower in the EC group (316 mmol/l h) than in the UD group (380 mmol/l h; $P = 0.008$).

Lactate

In the immediate postoperative period, the mean lactate concentration was significantly higher after electrocautery (3.4 mmol/l) than after ultrasonic dissection (2.0 mmol/l; $P < 0.01$). Within the first 9 h postoperatively, a peak of 6 mmol/l was reached in the EC group, followed by a decline to baseline. In contrast, the UD group did not reach a peak and remained at levels 1.4 and 2.1 mmol/l. The mean lactate values were significantly higher in the EC group than in the UD group until 48 h postoperatively. The total lactate concentration

was significantly higher in the EC group (AUC, 233 mmol/l h) than in the UD group (AUC, 112 mmol/l h; P = 0.008).

Glycerol

From the beginning, the mean glycerol concentration (a direct parameter for tissue ischemia) was significantly higher in the EC group (210 μmol/l) than in the UD group (104 μmol/l; P < 0.01). The EC group showed a gradual decline until 50 h after surgery. The animals treated with ultrasonic dissection showed a similar tendency, but the concentrations were lower and declined only from 104 to 47 μmol/l. The total glycerol concentration in the EC group (mean AUC, 7,438 μmol/l h) was almost two times higher than in the UD group (mean AUC, 4,169 μmol/l h; P = 0.008).

Lactate–pyruvate ratio

The mean calculated lactate–pyruvate ratio immediately after surgery was significantly higher in the EC group than in the UD group (105 vs. 30; P < 0.01). The EC group reached ratios comparable with those of the UD group at 50 h after surgery. The animals treated with ultrasonic dissection showed an almost straight curve, with ratios between 14 and 30. The mean values were significantly higher in the EC group than in the UD group until 34 h after surgery. The mean AUC of the lactate–pyruvate ratio was higher in the EC group than in the UD group (4,387 vs. 1,639; P = 0.011).

Lactate–glucose ratio

The mean calculated lactate–glucose ratio was significantly higher in the EC group than in the UD group (0.74 vs. 0.37; P < 0.01). A peak was reached 22 h after surgery, with a ratio of 1.8. Thereafter, it declined to values between 0.2 and 0.4. The animals treated with ultrasonic dissection had ratios between 0.2 and 0.4. The mean values were significantly higher in the EC group until 48 h after surgery. The mean AUC of the lactate–glucose ratio was significantly higher in the EC group than in the UD group. (59 vs. 21; P = 0.008; Table 1).

Discussion

The current study demonstrates that electrocautery causes more ischemic peritoneal tissue damage than ultrasonic dissection. Ultrasonic surgery had no effect or only a transient ischemic effect on peritoneal tissue and therefore fits well into the principia of “good surgical technique.”

Microdialysis was proved useful in continuously measuring peritoneal extracellular chemistry. The inserted semipermeable membrane allowed a continuous diffusion of molecules out of the peritoneal interstitional space fluid into the perfusate medium for the whole study period without any failure.

Extracellular concentrations of glucose, pyruvate, lactate, and glycerol are broadly used as indicators of tissue hypoxia (5–14). During ischemia, impaired blood flow decreases the delivery of glucose and oxygen to the tissue, forcing it to switch from aerobic to anaerobic metabolism (15; 16). The result is an increase in lactate, and if the glucose supply is inadequate, also a decrease in pyruvate level.

The rise in interstitional glycerol level is related to membrane phospholipid degradation, indicating tissue damage (7). Although hyperlactataemia frequently is used as an indicator of anaerobic metabolism (6), its accumulation also can be caused by other conditions such as hypermetabolism, alkalosis, hepatic failure, toxins, and sepsis (6; 17; 18). Therefore, the

lactate–pyruvate ratio is a more reliable tissue-specific indicator of visceral ischemia (6; 8–11; 14;18). It correlates with the redox potential (6) and is less susceptible to artefacts caused by alterations in the dialysate recovery rate (8). The immediate rise in the lactate–pyruvate ratio, reflecting sudden ischemia and inducing tissue necrosis, accords with the pathology of the coagulation injury.

The immediate rise in glycerol, another sensitive cell membrane marker for ischemia, further supports early cell damage. The lactate–glucose ratio provides an understanding of the qualitative relation between the ischemic glycolysis substrate and the end product and therefore is elevated in tissue ischemia (12). This elevation starts later than that of the lactate–pyruvate ratio, reaching a peak after 24 h, making the lactate–glucose ratio a less reliable parameter measuring early ischemia in this model. Within 48 to 72 h postoperatively, no difference was seen any longer between the two treatment groups, suggesting a rapidly developing but short-lasting ischemia and a rapid peritoneal healing response.

Table 1 Area under curve (AUC)

DIALYSATE	***UD* (*N*=9)**	***EC* (*n=9*)**	***P***
Glucose (mmol.hr/L)			
Mean	380.3	316.1	0.008
Range	357.1-395.6	282.2-354.3	
SD	11.57	22.43	
Lactate (mmol.hr/L)			
Mean	112.3	232.7	0.008
Range	96.5-155.0	185.8-276.0	
SD	22.2	36.9	
Glycerol (μmol.hr/L)			
Mean	4169.4	7437.6	0.008
Range	3162-4751	4778-8872	
SD	602.1	1210.1	
Lactate/Pyruvate Ratio			
Mean	1639.2	4387.0	0.011
Range	839.2-3307.0	2563-6734	
SD	768.9	1513.9	
Lactate/Glucose Ratio			
Mean	20.8	59.1	0.008
Range	17.3-29.2	44.1-70.5	
SD	4.2	8	

P values are for the differences between UD and EC
UD ultrasonic dissection, EC electrocautery, SD standard deviation

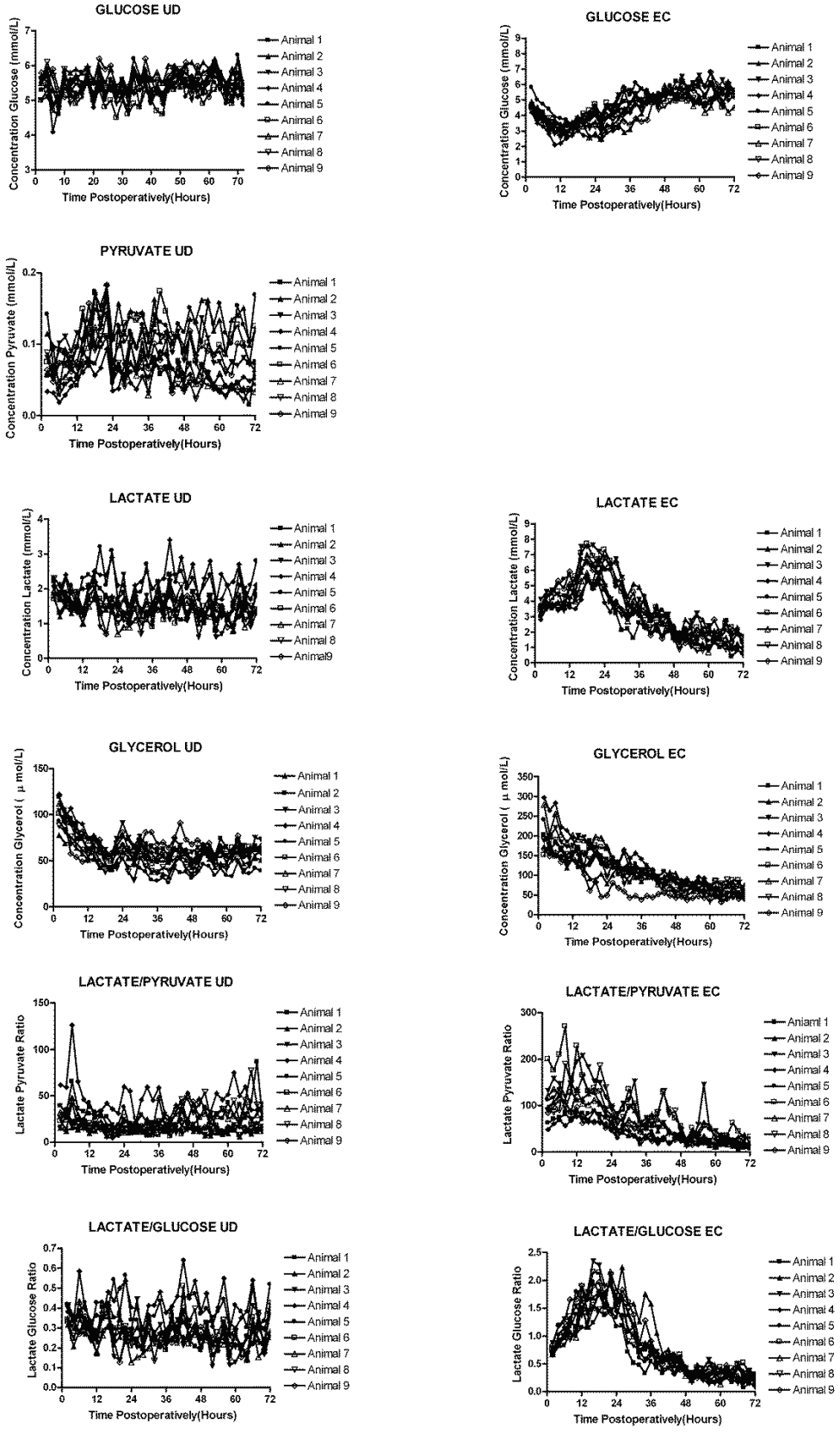

Figure 2 Unrefined data. Microdialysis parameters in animals that had surgery with ultrasonic dissection (UD) (n = 9) or electrocautery (EC) (n = 9).

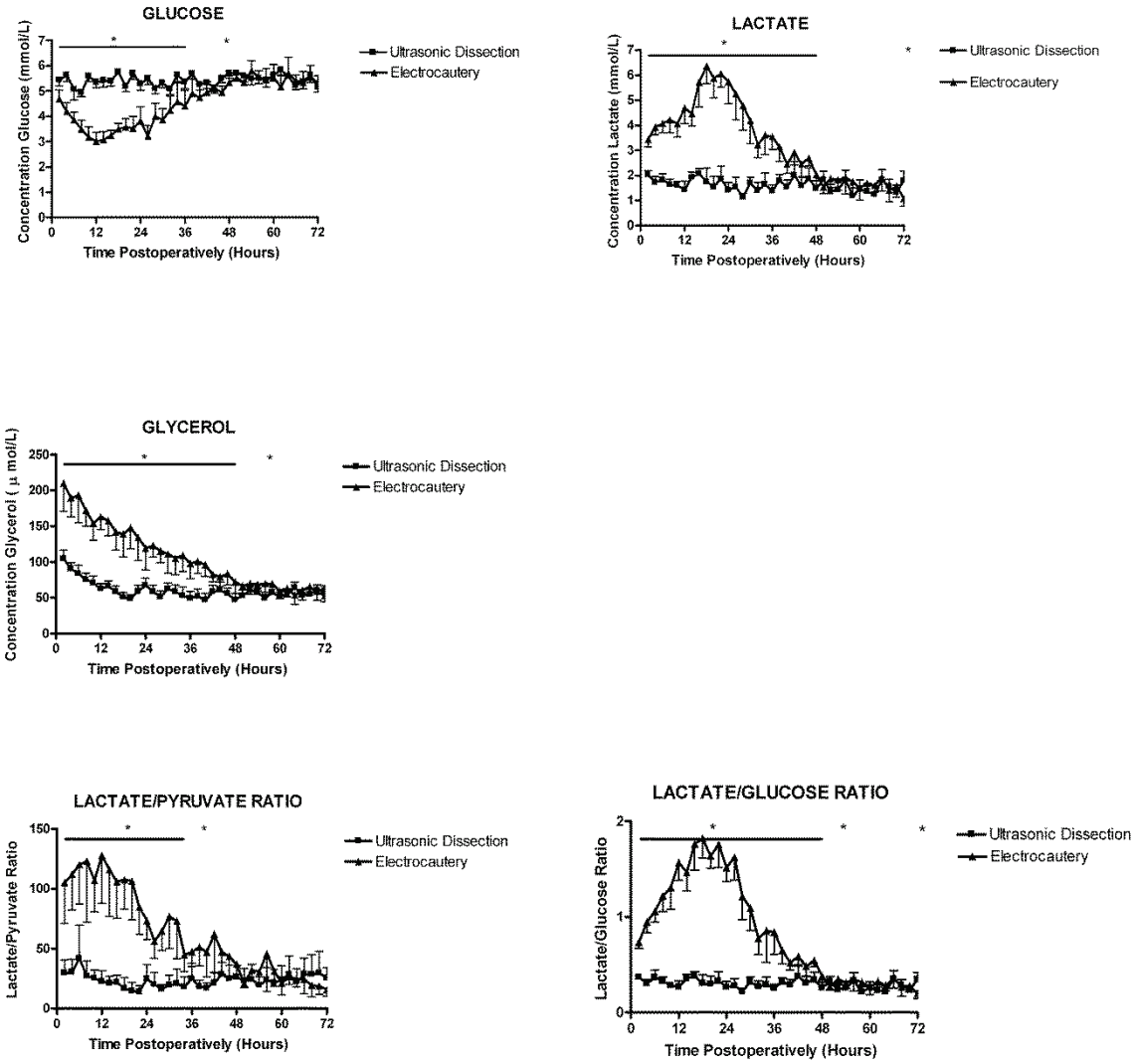

Figure 3 Microdialysis parameters in animals that had surgery with ultrasonic dissection (UD) (n = 9) or electrocautery (EC) (n = 9). Values are expressed as means and 95% confidence intervals. *P < 0.01.

Ultrasonic dissection caused almost no tissue damage in the current study. In an animal study of peritonitis, control subjects undergoing a sham operation (laparotomy and peritoneal insertion of a microdialysis catheter) showed patterns of ischemic indices corresponding with those of the ultrasonic group (19). Less injury by using ultrasonic dissection rather than electrocautery also was demonstrated in histologic biopsies of vascular endothelium, abdominal fascia, and bile duct (3; 20; 21). This accords with various clinical studies showing fewer gallbladder perforations during laparoscopic cholecystectomy, fewer symptomatic lymphoceles after paraaortic lymphadenectomy, less necrosis after flap reconstruction, and less postoperative pain after gynaecologic surgery and tonsillectomies, all explained by less tissue necrosis and inflammation (22–27).

Others have reported less favourable results with use of the ultrasonically activated scalpel related to high heat production, activation longer than 10 s, and slow cooldown after the instrument is turned off (4; 28). The use of a scalpel versus a hook, the duration of instrument

activation, the different tissues examined (well- vs. poor- vascularised tissue), and the tissue contact after application explain the differences in findings between studies. The short duration of peritoneal contact with a hook probably explains the more favourable outcome in our study than in the study of Kim et al (4). Lateral thermal injury also was less in pig intestine and abdominal wall when energy was applied with pauses in contrast to the continuous activation of the Harmonic Scalpel (29).

Placement of the catheter itself did not seem to influence the current data, as deduced from the minimal changes in the UD group. Because of catheter placement, we did not control for peritoneal tissue responses through measurements, for example, in the subcutaneous tissue, as many studies do. A previous study demonstrated the same pattern recorded over time for catheters placed intraperitoneally and subcutaneously (17).

In daily practice, electrocautery is more frequently used than ultrasonic dissection despite multiple clinical studies indicating a superiority of the latter in causing less tissue damage, as evidenced by a decrease in gallbladder and intestine perforations during surgery and a reduction in complication rates for various abdominal, vascular, cardiac, and plastic surgeries (15; 22–25; 30–38). The results of our study support a more frequent use of ultrasonic dissection in abdominal and pelvic surgery.

A favourable consequence of less tissue ischemia is the reduction in adhesion formation. Notably, the use of sutures was associated with a lower adhesion score compared with electrocautery in a small randomized controlled trial (39). Adhesion formation was not a primary end point in the current study because 3 days of microdialysis was too short for accurate scoring of adhesions. A longer duration of microdialysis was deemed hazardous because of an increased risk of catheter blocking and foreign body reaction, which would introduce adhesions.

It is concluded that the metabolic profiles in the current study resemble tissue ischemia with the use of ultrasonic surgery compared with electrocautery. In terms of optimal surgical technique, therefore, ultrasonic dissection is the preferred over electrocautery.

Acknowledgments

The authors gratefully acknowledge the expert advice of Jan Hendriks from the department of Epidemiology and Biostatistics, University of Nijmegen, The Netherlands.

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Part III: Adhesion prevention

Chapter 10: Benefits and harms of adhesion barriers for abdominal surgery: a systematic review and meta-analysis

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Published in: Lancet. 2014; 383: 48-59

Abstract

Background

Formation of adhesions after peritoneal surgery results in high morbidity. Barriers to prevent adhesion are seldom applied, despite their ability to reduce the severity of adhesion formation. We evaluated the benefits and harms of four adhesion barriers that have been approved for clinical use.

Methods

In this systematic review and meta-analysis, we searched PubMed, CENTRAL, and Embase for randomised clinical trials assessing use of oxidised regenerated cellulose, hyaluronate carboxy methylcellulose, icodextrin, or polyethylene glycol in abdominal surgery. Two researchers independently identified reports and extracted data. We compared use of a barrier with no barrier for nine predefined outcomes, graded for clinical relevance. The primary outcome was reoperation for adhesive small bowel obstruction. We assessed systematic error, random error, and design error with the error matrix approach. This study is registered with PROSPERO, number CRD42012003321.

Findings

Our search returned 1840 results, from which 28 trials (5191 patients) were included in our meta-analysis. The risks of systematic and random errors were low. No trials reported data for the effect of oxidised regenerated cellulose or polyethylene glycol on reoperations for adhesive small bowel obstruction. Oxidised regenerated cellulose reduced the incidence of adhesions (relative risk [RR] 0.51, 95% CI 0.31–0.86). Some evidence suggests that hyaluronate carboxymethylcellulose reduces the incidence of reoperations for adhesive small bowel obstruction (RR 0.49, 95% CI 0.28–0.88). For icodextrin, reoperation for adhesive small bowel obstruction did not differ significantly between groups (RR 0.33, 95% CI 0.03–3.11). No barriers were associated with an increase in serious adverse events.

Interpretation

Oxidised regenerated cellulose and hyaluronate carboxymethylcellulose can safely reduce clinically relevant consequences of adhesions.

Introduction

Adhesions are the most common cause of long-term complications from abdominal surgery. They can cause small bowel obstruction, injury at reoperations, female infertility, and chronic pain.(1- 5) Adhesions can affect the quality of life of millions of patients, jeopardise life expectancy, and result in more than US$2 billion dollars of health-care costs in the USA yearly.(2;6;7)

Steps are rarely taken to prevent adhesion despite evidence that adhesion barriers reduce their formation.(1;8-11) Underestimating the burden of adhesions seems to be an important explanation for the lack of use of adhesion barriers.(12) Unlike other postsurgery complications, the consequences of adhesion formation include various clinical entities that are often dealt with by specialists other than the surgeon who did the initial operation.(4; 5;7) Additionally, many questions exist about the indications for adhesion barriers, cost-effectiveness, and which barrier to use.(12;13)

Cochrane reviews have not answered the questions of efficacy and safety of barriers.(14-16) More than 20 different membranes and liquids have been investigated in clinical studies for use as adhesion barriers. Many were either unsuccessful in reducing the formation of adhesions or were only assessed using outcomes of little clinical importance.(17;18) Some were even associated with detrimental effects.(19) Results were dispersed over three reviews and only trials in gynaecological or colorectal surgery were included. Thus, appraising the available evidence about the use of adhesion barriers remains difficult.

The error matrix approach has been specifically developed for such situations, in which the possible benefits and harms of an intervention are difficult to summarise.(20) This approach consists of assessment of the three dimensions of systematic error, random error, and design error. The three dimensions of error can be presented in a three dimensional plot so that the relevance and strength of evidence for different benefits and harms can be judged at a single glance.

We assessed the benefits and harms of use of adhesion barriers for all types of abdominal surgery by such an approach.

Methods

Study design and systematic review

We assessed the results of our systematic review and meta-analyses by the error matrix approach. The error matrix approach has been validated in systematic reviews of cholecystectomy and inguinal hernia repair.(21;22) We included randomised trials evaluating the four adhesion barriers that have been approved for clinical use by legislative authorities in Europe and the USA: hyaluronate carboxymethylcellulose (Seprafilm®, Sanofi, Paris, France), oxidised regenerated cellulose (Interceed®, Johnson & Johnson, New Brunswick, NJ, USA), icodextrin 4% solution (Adept®, Baxter, Deerfield, IL, USA), and polyethylene glycol (Spraygel®, Sprayshield®, Confluent Surgical, Waltham, MA, USA).

We searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials with Mesh descriptors including: “carboxymethylcellulose”, “hyaluronic acid”, “icodextrin”, “polyethylene glycols”, “tissue adhesions”, “intestinal obstruction”, “infertility, female”, “abdominal pain”, “pelvic pain”, and “intestinal disease/surgery”. The appendix shows the full search strategy. We did not apply any language restrictions and included all relevant

articles up to Feb 2, 2013. Only randomised trials were included. We also searched the reference lists of identified trials, for further references, including those published in grey literature. We did additional searches to find relevant grey literature and unpublished trials (appendix).

RPGtB and MWJS identified eligible reports; discrepancies were resolved through discussion. We applied the following inclusion criteria to the titles and abstracts of the search results: patients undergoing intraperitoneal surgery, application of one of the four adhesion barriers, and report of adhesion-related outcomes. Results of some trials were reported in more than one report. Information from the different reports was linked and analysed as a single trial.

We assessed all trials for the risk of bias (measured by the level of evidence), the risk of random error, and the design error.(20) We present data in a three-dimensional Manhattan plot. We assessed the risk of systematic error with the Cochrane Collaboration's instrument for bias risk assessment.(23) Six components associated with the risk of bias were assessed: generation of the allocation sequence, allocation concealment, masking of outcome assessors, selective outcome reporting, incomplete follow-up, and other potential sources of bias. Trials with a low risk for all six components were defined as having an overall low risk of bias. Trials in which one or more of the six bias components were unclear or had high risk of bias were defined to be at high risk of bias. Because masking the surgeon to allocation is impossible, trials in which patients and outcome assessors were masked were deemed to have a low risk of bias for masking. Additionally, we recorded data about funding sources.

The risk of random error is the risk of drawing a false conclusion based on sparse data. This risk is quantified as the p value. However, because random low (and random high) p values might occur during accumulation of data and sequential testing, they do not sufficiently represent the risk of random error between different studies.(24) The standard error (SE) measures the amount of variability in the sample mean; it indicates how closely the population mean is likely to be estimated by the sample mean. We therefore used SE to evaluate the risk of random error, using the algorithms suggested by the Cochrane collaboration.(23) We defined small risk of random error as an SE of less than 0.20 and moderate risk as an SE of less than 1.00. Studies with higher risk of random error ($\geq$1.00) fell outside the range of the plot.

We assessed design error (external validity) by classifying the clinically relevant outcome measures according to the Grading of Recommendations Assessment, Development and Evaluation approach.(25) We assessed publication bias with funnel plots. Raw data from unpublished studies and studies using adhesion-related outcomes other than those predefined were reported separately.

We compared use of a barrier with no barrier for nine predefined outcomes. The primary outcome was reoperation for adhesive small bowel obstruction. We also assessed serious adverse events, total incidence of adhesions, reoperation time, small bowel obstruction from any cause, site-specific incidence of adhesions, and adhesion score.

Statistical analysis

We used the Mantel-Haenszel method for dichotomous data, presented as relative risks (RR) with 95% CIs. We used the inverse variance method to pool continuous data; results are presented as standardised mean difference with 95% CIs. We assessed statistical

heterogeneity with Cochran's test and I2. In the absence of statistical heterogeneity we used a fixed-effect model, otherwise we used a random-effects model. We did the analyses with Review Manager (version 5.1) and R (version 2.12.0). (26)

We did three subgroup analyses. First, we compared the pooled results of trials with a low overall risk of bias with the pooled results from trials with a high overall risk of bias. Second, we compared the pooled results of trials with a low risk of funding bias with trials with an unclear or high risk for funding bias (trials sponsored by industry). Third, trials with clinical heterogeneity were not pooled into one overall effect estimate. Clinical heterogeneity was assessed by subgroup according to the type of operation (upper alimentary tract, lower alimentary tract or colorectal, abdominal wall, gynaecological, or urological surgery). All subgroup analyses were tested for interactions.

The full review protocol is registered with PROSPERO (number CRD42012003321) and shown in the appendix.

Role of the funding source

There was no funding source for this study. RPGtB and HvG had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Our search returned 1840 results, from which we included 33 trials assessing 5381 patients in our systematic review (Fig 1, table 1). Five trials either reported on outcomes not included in the predefined outcomes or had incomplete outcome data. Thus, 28 trials assessing 5191 patients were included in the meta-analyses. 20 trials were of gynaecological surgery, nine of colorectal surgery, and one each of gastric, hepatic, general paediatric, and small bowel obstruction surgery.

Outcome measures were reoperation for adhesive small bowel obstruction (six trials), serious adverse events (14 trials), overall incidence of adhesions (six trials), operation time (three trials), small bowel obstruction by any cause (five trials), site-specific incidence of adhesions (ten trials), and adhesion score (13 trials). These outcome measures were ranked according to their clinical relevance for the patient according to Grading of Recommendations Assessment, Development and Evaluation with reoperation for adhesive small bowel obstruction as the highest relevance and adhesion score as the lowest (table 2).

Roughly two-thirds of trials adequately generated an allocation sequence (Fig 2). Most studies had adequate allocation concealment and masking of the outcome assessors. Follow-up methods and description of reasons for loss to follow-up were adequate in the majority of trials. The risk of outcome bias through selective reporting was low for some studies. The primary endpoint was changed during one trial.(53) The timing of second look procedures varied widely in the study by Tinelli and colleagues.(11) One trial was stopped prematurely because of organisational difficulties.(57)

Overall, four trialshad a low risk of bias based on all six domains (figure 2). (1;8;9;55)

Industry sponsored 16 trials (57%) and sponsoring was not reported for seven trials (25%). Two trials assessing hyaluronate carboxymethylcellulose were initiated and sponsored by independent parties.(39;42) Another three trials were investigator driven, but the manufacturer supplied the adhesion barrier.(38;48;57) The results from investigator-driven trials were similar to the results from industry-sponsored trials (appendix).

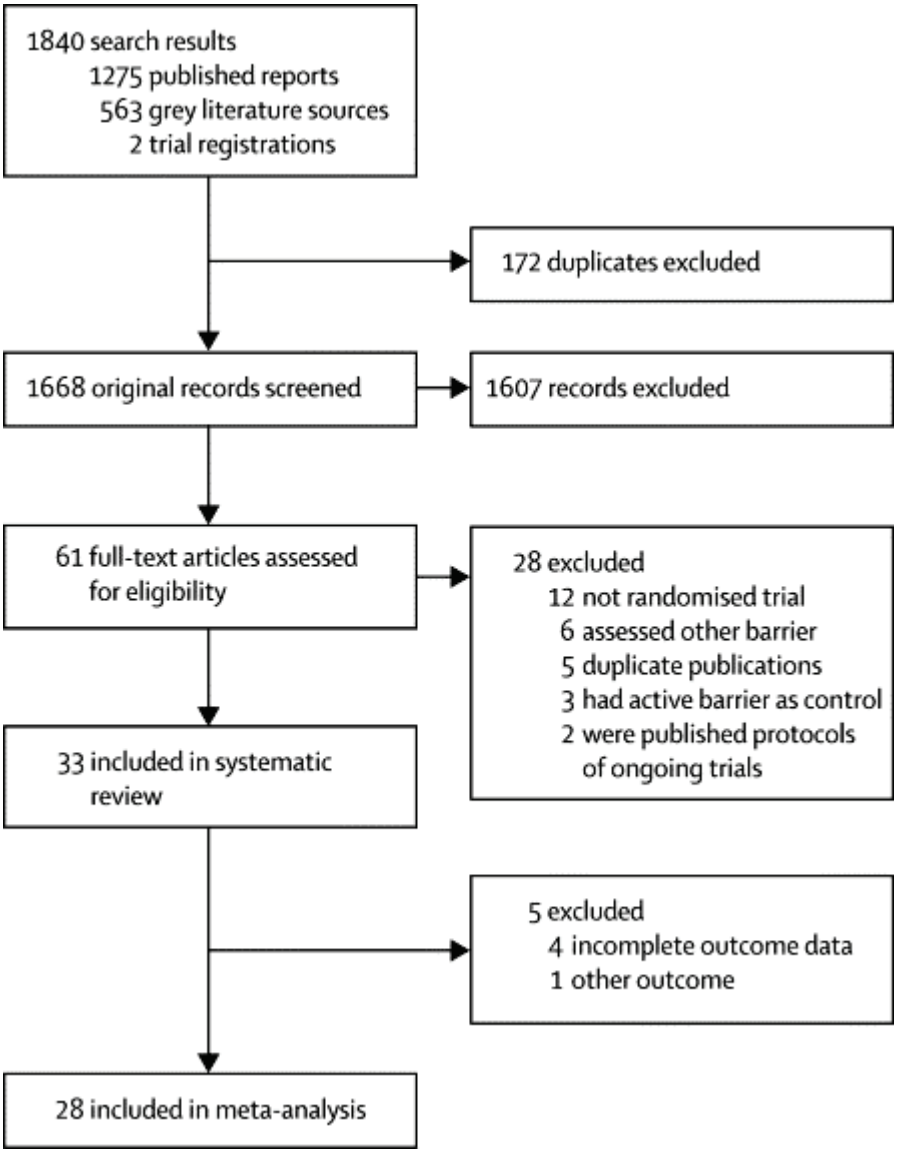

Figure 1 Study selection

The risk of random error (SE) was small for adhesion score in eight trials, and overall incidence of small bowel obstruction by any cause in one trial. Funnel plots appeared to be symmetrical: trials did not report extreme values (outside 95% CI) by most analyses (appendix). Three additional trials from grey literature and trial registries had limited available outcome data. Their findings accorded with the results of published studies (appendix).

Table 1 Trials included in systematic review

Trial	design	Area	randomised	Patients	intervention	control	outcome	funding
Oxidized regenerated cellulose								
[Nordic Adhesion Prevention Study Group] (1995)	multicentre (8 hospitals, 2 countries)	Gynaecological	66 pts; unit of randomization: ovaries	Female infertility patients with bilateral tubal disease undergoing complete adhesiolysis	adnex and fallopian tube covert with sheet of oxidized regenerated cellulose	other side was left uncovered	Site specific adhesions; adhesion score	Johnson & Johnson AB, Stockholm, Sweden
Azziz (1993)	multicentre (13 hospitals)	Gynaecological	134 pts; unit of randomization: pelvic sidewall	Female patients undergoing fertility surgery requiring bilateral adhesiolysis	One sheet of oxidized regenerated cellulose was applied to one sidewall after complete adhesiolyis	other sidewall was left uncovered	Site specific adhesions	Partial grant from Johnson & Johnson incorporate.
Franklin (1995)	multicentre (13 hospitals)	Gynaecological	57 pts; unit of randomization: ovaries	Female infertility patients with bilateral tubal disease undergoing complete adhesiolysis	One sheet of oxidized regenerated cellulose was applied to one ovary	other side was left uncovered	Site specific adhesions; adhesion score	Johnson & Johnson Medical inc, Arlington, Texas.
Geldrop (1994)*	Unknown	Gynaecological	20 pts; unit of randomization: ovaries	female patients undergoing bilateral ovarian surgery	One sheet of oxidized regenerated cellulose was applied to one ovary	other side was left uncovered	Adhesion score -abstract only, incomplete data-	Not reported
Greenblatt (1993)	single centre	Gynaecological	8 pts; unit of randomization: ovaries	female patients undergoing fertility surgery for polycystic ovarian disease	One sheet of oxidized regenerated cellulose was applied to one ovary	other side was left uncovered	adhesion score	Medical research council of Canada and Ethicon (a Johnson & Johnson company)
Keckstein (1996)	open-label single centre	Gynaecological	25 pts; unit of randomization: ovaries	Female patients undergoing bilateral ovarian cystectomy	One sheet of oxidized regenerated cellulose was applied to one ovary	other side was left uncovered	Site specific adhesions	Johnson & Johnson medical inc.
Li (1994)	single centre	Gynaecological	28 pts; unit of randomization: pelvic sidewall	Female patients undergoing bilateral pelvic adhesiolysis	One sheet of oxidized regenerated cellulose was applied on to one sidewall after complete adhesiolyis	other sidewall was left uncovered	adhesion score	Johnson & Johnson medical Ltd, provided adhesions barriers and financial support
Mais (1995a)	single centre	Gynaecological	32 pts.	Premenopausal women undergoing laparoscopic endometriosis surgery	Operated area was covered with one to three sheets of oxidized regenerated cellulose	No barrier	Incidence of adhesions	Not reported
Mais (1995b)	single centre	Gynaecological	50 pts.	Premenopausal women undergoing laparoscopic myomectomy	Operated area was covered with three sheets of oxidized regenerated cellulose	No barrier	Incidence of adhesions; adhesion score	Not reported
Saravelos (1996)	single centre	Gynaecological	27 pts; unit of randomization: ovaries	Female patients undergoing laparoscopic fertility surgery for polycystic ovarian disease	One sheet of oxidized regenerated cellulose was applied to one ovary	other sidewall was left uncovered	Site specific adhesions; adhesion score	Johnson & Johnson medical Ltd, provided adhesions barriers and financial support
Sekiba (1992)	multicentre (12 hospitals)	Gynaecological	63 pts; unit of randomization: pelvic sidewall	Female patients undergoing laparotomy for endometriosis	One sheet of oxidized regenerated cellulose was applied to one sidewall after complete adhesiolyis	The other sidewall was left uncovered	Site specific adhesions	Partial grant from Johnson & Johnson
Tinelli (2011)	multicentre	Gynaecological	694 pts	Female patients undergoing open or	Operative area covered by sheets of	No barrier	Incidence of	Not reported, No

				laparosocpic myomectomy	Oxidized regenerated cellulose		adhesions, serious adverse events	conflicts of interests declared in financial disclosure
Hyaluronate carboxymethylcellulose								
Beck (1997)	multicentre	Colorectal	183 pts	Patients undergoing open colectomy and ileal J-pouch anal anastomosis	Hyaluronate carboxymethylcellulose (on average little more than 2 sheets)	No barrier	Site specific adhesions; adhesion score, serious adverse events	Not reported, one contributing author working for Genzyme corporation
Diamond (1996)	multicentre (19 hospitals)	Gynaecological	127 pts	Female patients undergoing open myomectomy surgery	One up to two sheets of Hyaluronate carboxymethylcellulose	No barrier	Adhesion score	Genzyme corporation
Dupré (2013)	Multicentre (8 hospitals)	Hepatic surgery	54 pts	Patients undergoing two- stage liver resection	Four sheets of Hyaluronate carboxymethylcellulose between liver lobes	No barrier	Adverse events; Reoperation for ASBO; operation time	Ministry of Health, France. Bariers provided by Genzyme
Fazio (2006)	multicentre, multinational single blinded	Colorectal	1791 pts	Open colorectal surgery for benign disease	Hyaluronate carboxymethylcellulose	No barrier	Reoperation for ASBO; SBO (any cause), serious adverse events	Genzyme Corporation
Hayashi (2008)	multicentre (3 hospitals)	Gastric	150 pts	Patients undergoing gastrectomy for malignant disease	Hyaluronate carboxymethylcellulose	No barrier	Reoperation for ASBO; SBO (any cause), serious adverse events	Nihon University
Inoue (2005)	Single centre	General pediatric	122 pts	Various procedures in general surgery in pediatric patients	Hyaluronate carboxymethylcellulose	No barrier	Post hoc analysis of operative time from 17 patients	Not reported
Kusunoki (2005)	multicentre (3 hospitals)	Colorectal	62 pts	Patients undergoing open surgery for rectal malignancy	Hyaluronate carboxymethylcellulose	No barrier	Reoperation for ASBO; SBO (any cause) Site specific adhesions	Not reported
Park (2009)	single centre study	Colorectal	427 pts	Patients undergoing radical resection for rectal or sigmoid cancer	Hyaluronate carboxymethylcellulose	No barrier	Reoperation for ASBO; SBO (any cause), serious adverse events	IN-SUNG foundation for Medical research
Salum (2006)	multicentre (15 hospitals)	Colorectal	191 pts	Patients undergoing colorectal surgery with temporary ileostomy	Hyaluronate carboxymethylcellulose	No barrier	Site specific adhesions; adhesion score, serious adverse events	Genzyme Corporation
Vrijland (2002) / Van der Wal (2011)	multicentre (10 hospitals)	Colorectal	67 pts	Patients undergoing open Hartmann's procedure	Hyaluronate carboxymethylcellulose	No barrier	Site specific adhesions, serious adverse events, Chronic abdominal complaints	Not reported
Icodextrin								
Catena (2011)	single centre	Adhesive bowel obstruction	181 pts	Patients operated for adhesive small bowel obstruction	Icodextrin	No barrier	Reoperation for ASBO; small	Baxter BioSurgery (Italy)

							bowel obstruction(any cause), serious adverse events	
diZerega (2002)	open-label multicentre (5 hospitals)	Gynaecological	62 pts	Female patients undergoing laparoscopy for infertility or chronic pelvic pain	Icodextrin	No barrier	Incidence of adhesions	Not reported
Kossi (2009)	double blinded single centre	Colorectal	23 pts	Patients undergoing Hartmann's procedure	Icodextrin	Ringers lactate solution as placebo	Operation time, serious adverse events	Iinvestigator driven. Limited support from Shire pharmaceuticals/ Baxter BioSurgery
Trew (2011)	double blinded multicentre (25 hospitals)	Gynaecological	498 pts	Female patients undergoing removal of myomas or endometriotic cysts	Icodextrin	Ringers lactate solution as placebo	Adhesion score, serious adverse events	Baxter BioSurgery
PEG adhesion barrier								
Banasiewicz (2011)*	Multicentre	Colorectal	11 pts	Patients undergoing colorectal surgery	PEG adhesion barrier	Not reported	Adhesion score, Operative time - abstract only, data incomplete-	Confluent Surgical inc.
De Wilde (NA)*	Multicentre	Gynaecological	15 pts	Female patients undergoing laparoscopic resection of fibroid or myoma	PEG adhesion barrier	Not reported	Incidence of adhesions - abstract only, data incomplete-	Confluent Surgical inc.
Johns (2003)*	Single centre	Gynaecological	22 pts	Female patients undergoing bilateral adnexal surgery	PEG adhesion barrier	No barrier	Extent of adhesions	Confluent Surgical inc.
Mettler (2008)	multicentre (6 hospitals, 3 countries)	Gynaecological	72 pts	Female patients undergoing open or laparoscopic myomectomy	PEG adhesion barrier	Ringers lactate solution as placebo	Adhesion score, serious adverse events	Angiotech Pharmaceuticals
Mettler (2004)	multicentre (2 hospitals)	Gynaecological	64 pts	Female patients patients undergoing open or laparoscopic myomectomy	PEG adhesion barrier	No barrier	Incidence of adhesions	Not reported
Tjandra (2008)	single centre	Colorectal	40 pts	Patients undergoing low anterior resection or ileal pouch anal anastomosis with temporary loop ileostomy	PEG adhesion barrier	No barrier	adhesion score; operation time, serious adverse events	Confluent Surgical inc.
Ten Broek (2012)	single centre	Gynaecological	15 pts	Female patients undergoing laparoscopic treatment of benign gynaecological disease	PEG adhesion barrier	No barrier	Incidence of adhesions; adhesion score, serious adverse events	Investigator driven. Limited support from Confluent Surgical inc.

ASBO= adhesive small bowel obstruction, SBO= small bowel obstruction. *Not included in meta-analaysis.

Table 2 Predefined outcomes ranked according to Grading of Recommendations Assessment, Development and Evaluation by relevance according to the patients' perspective

Critical for decision making	9	Reoperation for adhesive small bowel obstruction
	8	Serious Adverse Events
Important for decision making	6	Total incidence of adhesions
	5	Operation time of reoperation
	4	Small bowel obstruction(any cause)*
Limited importance	2	Site specific incidence of adhesions
	1	Adhesion score

* Includes small bowel obstructions not caused by adhesions

Oxidised regenerated cellulose is a solid barrier in the form of a knitted fabric. After application on the injured peritoneum it swells and becomes a gel. The gel breaks down to monosaccharides and is metabolised by glycosidases of peritoneal macrophages within 4 days to 2 weeks.(58;59) Oxidised regenerated cellulose was compared with no adhesion barrier in 11 trials (1184 patients).(8;9;11;27- 29;31-35) All trials were of gynaecological patients. Two trials had low risk of bias.(8;9) Eight trials were explicitly industry-sponsored and sponsorship was unclear for three trials. In eight studies (408 patients), each patient served as their own control by having one side of the pelvis randomly assigned to receive an adhesions barrier. The remaining three trials included 776 patients in a parallel group design.

Figure 3 shows the results of our meta-analysis. Figure 4 shows overall results from the included trials of oxidised regenerated cellulose. No trials reported data for the effect of oxidised regenerated cellulose on reoperations for adhesive small bowel obstruction. Evidence shows the beneficial effects of oxidised regenerated cellulose on the incidence of adhesions and adhesion scores from trials with low risks of both systematic and random error. No evidence exists for a beneficial effect on the incidence of serious adverse events (appendix).

No trials reported data for pregnancy rate with oxidised regenerated cellulose. Incidence of serious adverse events after myomectomy was much the same between the two groups in one trial (RR 0.80, 95% CI 0.46–1.39).(11) Postoperative fever was the only serious adverse event recorded in both groups.

With regard to outcomes important for decision making, the overall incidence of adhesions reported by three trials (578 patients) was significantly reduced in the treatment group (RR 0.51, 95% CI 0.31–0.86; Fig 3) with a number needed to treat of 6 (95% CI 3.37–21.00). The intervention effect increased when only trials with low risk of bias were assessed. No data were available for operation time and small bowel obstruction for any cause. Use of oxidised regenerated cellulose significantly reduced the site-specific incidence of adhesions (RR 0.66, 95% CI 0.59 to 0.74) and adhesion scores (standardised mean difference [SMD] −3.74, 95% CI −5.71 to −1.77).

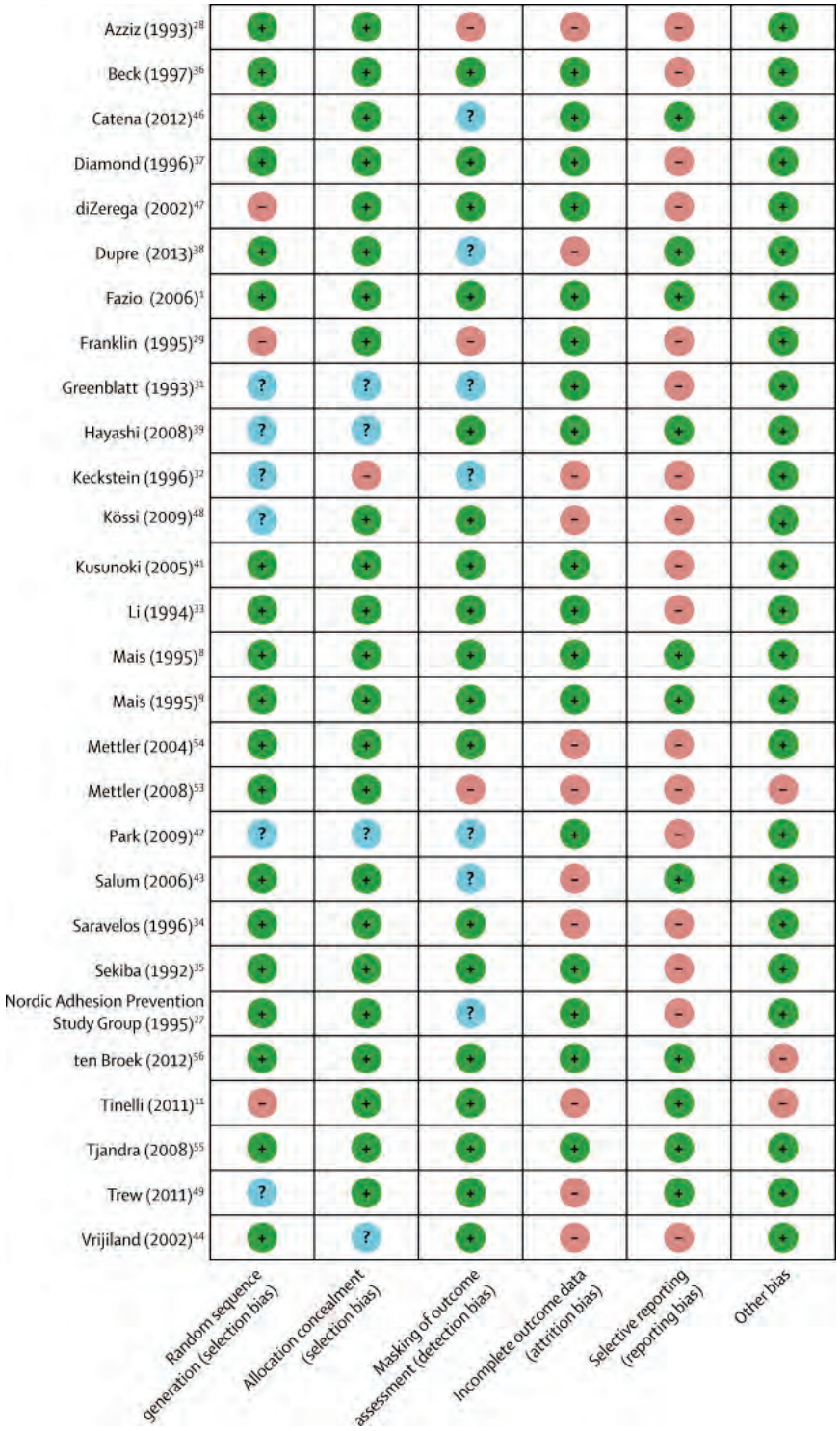

Figure 2 Methodological quality of trials included in meta-analysis.

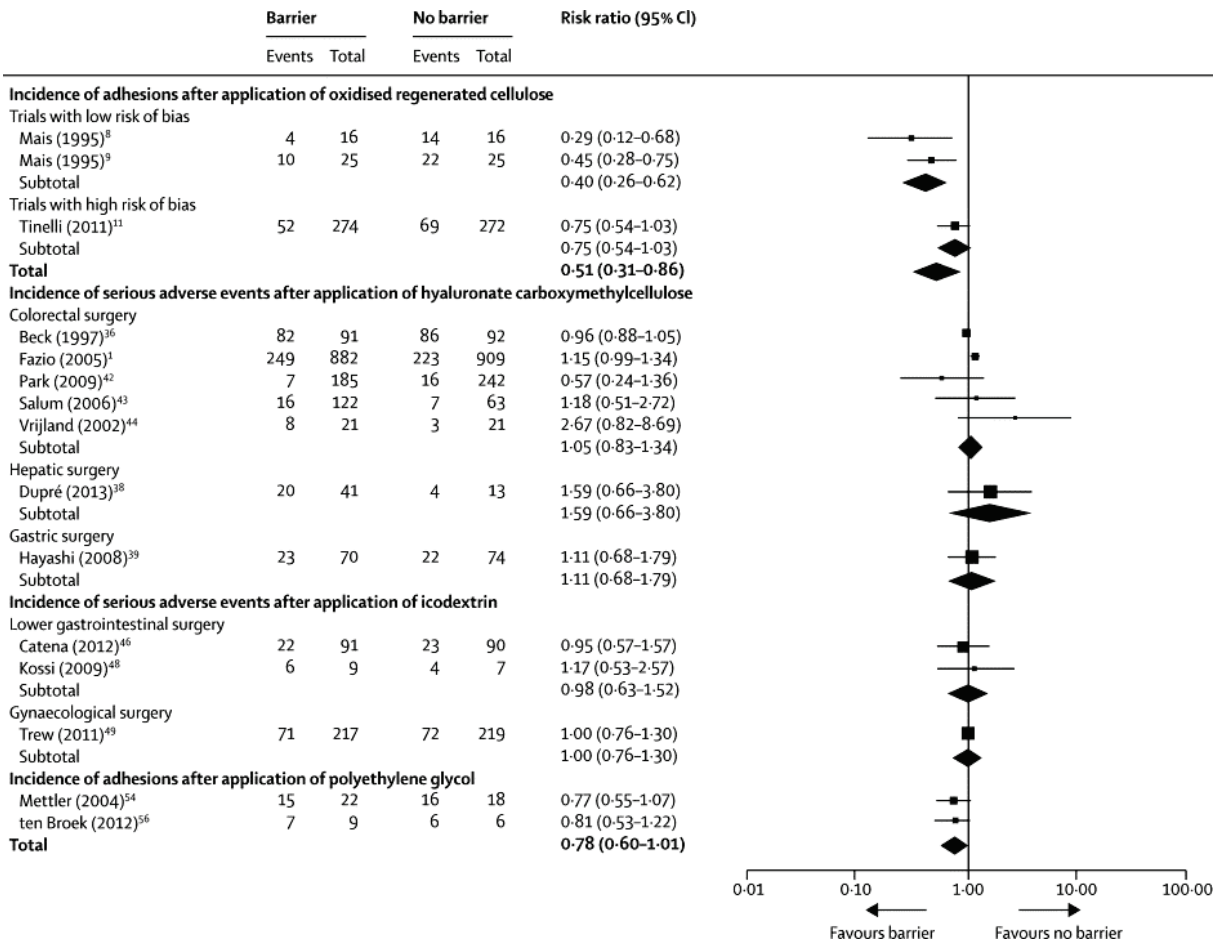

Figure 3 Results of key comparisons of four adhesion barriers

Random effect applied for the incidence of adhesions after application of oxidised regenerated cellulose and the incidence of serious adverse events after application of hyaluronate carboxymethylcellulose; fixed effects applied for the incidence of serious adverse events after application of icodextrin and the incidence of adhesions after application of polyethylene glycol. Only subtotals were pooled for hyaluronate carboxymethylcellulose and icodextrin because of heterogeneity in types of operations. The appendix shows forest plots for other comparisons.

Hyaluronate carboxymethylcellulose is a solid adhesion barrier in the form of a thin translucent membrane. The membrane adheres well to moist tissue surfaces and forms a viscous gel in 1–2 days. The barrier is absorbed from the abdominal cavity within 7 days, and is metabolised and cleared via the kidney in a maximum of 28 days.(60)

Nine trials (3052 patients) assessed hyaluronate carboxymethylcellulose (1517 patients) compared with no adhesion barrier (1535 patients).(1;36-39;41-44) One trial had risk of low bias.(1) Three trials were investigator driven, four were sponsored by industry, and in two trials the sponsor was not specified. Six trials were of colorectal surgery and one each was of gynaecological, hepatic, and gastric surgery.

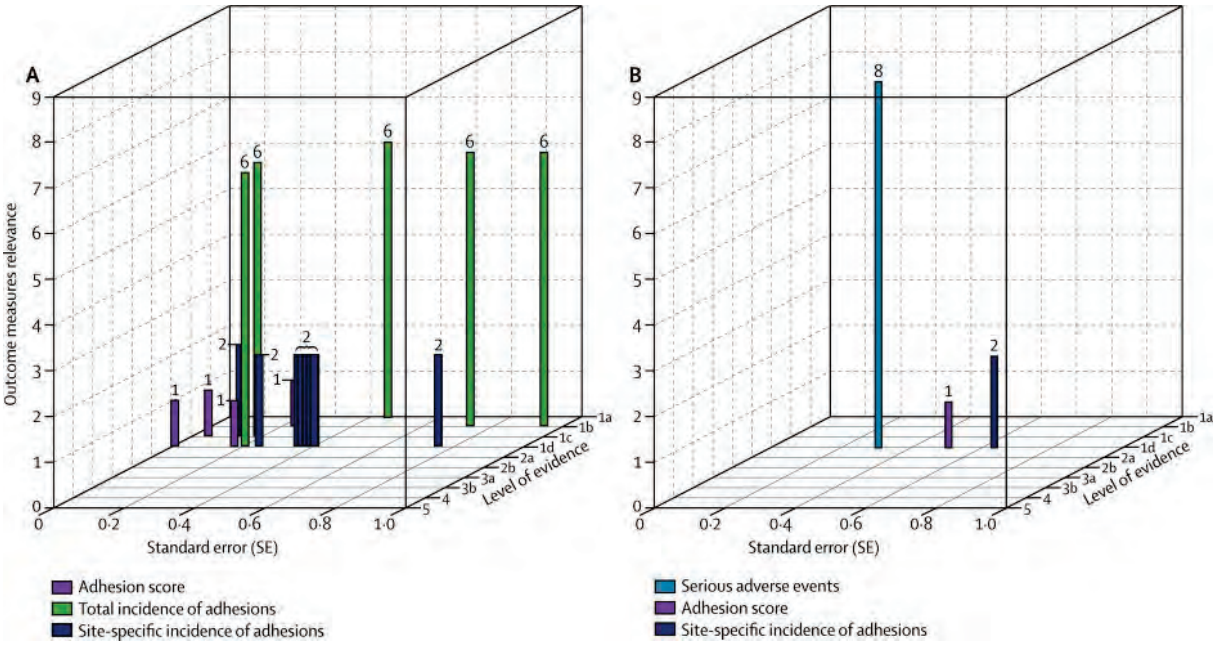

Figure 4 Outcomes of oxidised regenerated cellulose versus no adhesion barrier

Benefit (A) and no effect or harm (B). Systematic error: 1a is meta-analysis of low-bias risk randomised controlled trial, 1b a low-risk bias randomised controlled trial, 1c is meta-analysis of all randomised controlled trials, and 1d a high-risk bias randomised controlled trial. Standard error less than 0.20 is low risk for random error, 0.20–1.00 is moderate risk, and greater than 1.00 is high risk. Studies with a high risk for random error are outside the range and are considered irrelevant for decision making. Results most important for clinical decision making are the highest bars in the upper-left part of the plot.

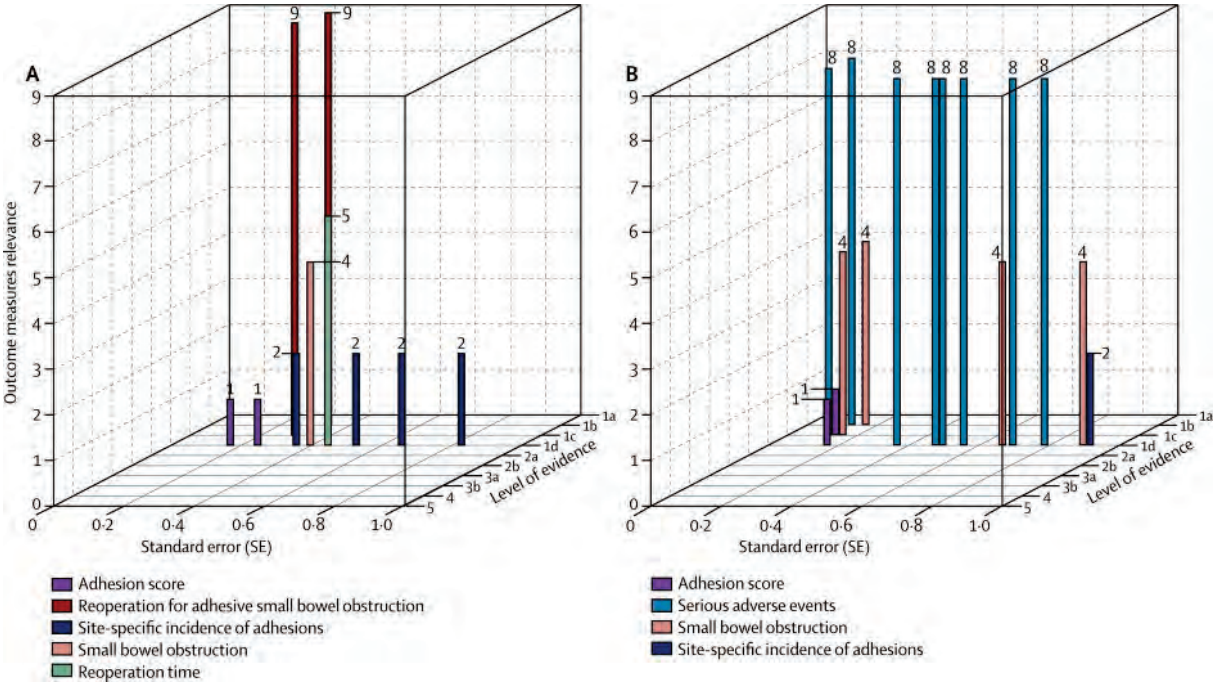

Figure 5 Outcomes of hyaluronate carboxymethylcellulose versus no adhesion barrier
Benefit (A) and no effect or harm (B)

Figure 5 shows overall results for hyaluronate carboxymethylcellulose. Some evidence suggests that hyaluronate carboxymethylcellulose reduces the incidence of reoperations for adhesive small bowel obstruction. Five trials evaluated this outcome, three in colorectal surgery, and one each in hepatic and gastric surgery. Hyaluronate carboxymethylcellulose significantly reduced the incidence of reoperations for adhesive small bowel obstruction in colorectal surgery (RR 0.49, 95% CI 0.28–0.88). The difference in the incidence of reoperation related to adhesive small bowel obstruction was not significant in hepatic surgery (RR 0.13, 95% CI 0.01–2.95) and gastric surgery (RR 0.35, 95% CI 0.01–8.50). Operation time also seems to be reduced by use of hyaluronate carboxymethylcellulose.

Seven trials studied the incidence of serious adverse events, five for colorectal surgery and one each for hepatic and gastric surgery. Differences between groups for the incidences of serious adverse events were all non-significant (figure 3).

A post-hoc analysis of one trial with low risk of bias showed that hyaluronate carboxymethylcellulose wrapped around a new bowel anastomosis seemed to result in a higher incidence of serious adverse events: abscesses, fistulas, and anastomotic leakages.(1) In more recent trials, the practice of wrapping hyaluronate carboxymethylcellulose around anastomoses has been abandoned.(39;42) There were no data for pregnancy rate.

In one trial of hyaluronate carboxymethylcellulose investigating two-stage hepatic surgery, operation time was significantly shorter in the hyaluronate carboxymethylcellulose group at reoperation (SMD −2.30, 95% CI −3.16 to −1.43). We report no significant difference for the outcome of small bowel obstruction from any cause in either gastric or colorectal surgery.

Our meta-analysis showed that hyaluronate carboxymethylcellulose significantly reduced the incidence of site-specific adhesions (RR 0.71, 95% CI 0.54–0.95). Adhesion score was significantly reduced in one trial of gynaecological surgery (SMD −1.41, 95% CI −1.80 to −1.02), but not for colorectal surgery (−0.86, −1.96 to 0.24).

Icodextrin is a water-soluble glucose polymer derived from cornstarch. It is a liquid adhesion barrier in a 4% solution. Before the icodextrin breaks down into oligosaccharides and is metabolised, the colloidal osmotic activity causes the fluid to reside in the abdominal cavity for 3–5 days.(61;62)

Four trials (764 patients) randomly assigned patients to icodextrin (386 patients), no adhesion barrier (90 patients), or placebo (282 patients).(46-49) The study of Kössi and colleagues was unclear about whether six patients were allocated to treatment or control.(48) No trials had a low risk of bias.

Most outcome data were not included in the Manhattan plot because of the high risk of random errors (appendix). Reoperation for adhesive small bowel obstruction did not differ significantly between groups (RR 0.33, 95% CI 0.03–3.11). Icodextrin has no beneficial effects on the number of serious adverse events (Fig 3). There is evidence of a moderate risk for random error that icodextrin reduces the incidence of small bowel obstruction. There is insufficient evidence to assess whether icodextrin has a beneficial effect on the incidence of adhesions or operation time (SMD −0.48, 95% CI −1.44 to 0.49).

Incidence of serious adverse events was similar among the groups in gynaecological surgery (RR 1.00, 95% CI 0.76–1.30) and lower alimentary tract surgery (0.98, 0.63–1.52).(46;48;49) There were no data for pregnancy rate.

Overall incidence of adhesions and operation time did not differ significantly for icodextrin. Icodextrin significantly reduced the incidence of small bowel obstruction by any cause (RR 0.20, 95% CI 0.04–0.88). There were no data for incidences of site-specific adhesions and we report no significant difference for adhesion score (SMD −0.29, 95% CI −2.97 to 2.39).

The polyethylene glycol adhesion barrier consists of two liquid precursor solutions that quickly react after being sprayed in the abdomen, forming a hydrogel. One of the precursors

contains a small amount of methylene blue, enabling the area covered and the thickness of the hydrogel layer to be seen during laparoscopy. The gel is degraded through hydrolysation and cleared via the kidneys in around 7–8 days.(63)

Four trials (191 patients) assessed polyethylene glycol in 111 patients and placebo in 80 patients.(53;54;55) One trial had a low risks of bias for all six bias risk domains.(55) No data were available for reoperation for adhesive small bowel obstruction. No data were available about the effect of polyethylene glycol on pregnancy rate. The incidence of serious adverse events did not differ in three trials of gynaecological surgery (RR 0.55, 95% CI 0.16–1.87) and colorectal surgery (1.11, 0.43–2.85).

Groups did not differ significantly for incidence of adhesions (RR 0.78, 95% CI 0.60 to 1.01). Polyethylene glycol had a beneficial effect on operation time in one trial with a low risk of systematic error (SMD −0.84, 95% CI −1.49 to −0.19). No data were available for small bowel obstruction by any cause and incidence of site-specific adhesions.

Polyethylene glycol significantly reduced adhesion scores both in gynaecological surgery (SMD −0.71, 95% CI −1.21 to −0.22) and in one trial of colorectal surgery with low risk of bias (SMD −1.71, 95% CI −2.45 to −0.97); however, the studies assessing these outcomes had high risk of random error.

Discussion

Sufficient evidence exists to suggest that oxidised regenerated cellulose and hyaluronate carboxymethylcellulose reduce adhesion formation. There is evidence that hyaluronate carboxymethylcellulose reduces the number of reoperations for adhesive bowel obstruction and operative time. Oxidised regenerated cellulose reduces the incidence of adhesions in gynaecological surgery, but no data were available about the effect on reoperations for adhesive bowel obstruction. Icodextrin had no effect on the incidence of reoperation for adhesive small bowel obstruction in one small trial, and no data for the primary outcome were available for polyethylene glycol. None of the four barriers investigated increased serious adverse events.

28 trials had been done, which is high for surgical research. Detailed assessment of the risk of bias showed that these trials had a low risk of both systematic and random errors compared with other surgical research—eg, robotic surgery, laparoscopic cholecystectomy, and fast-track surgery.(22;64)

Despite the large number of trials, outcome comparisons included only a few trials and results per comparison can easily be dominated by a single large trial. The different types of barrier used, the large clinical heterogeneity, and the different outcome parameters reported, hinder the pooling of results from multiple trials and made subgroup analyses necessary. Therefore, we assessed the potential benefits and harm of adhesion barriers by the error-matrix approach with visualisation in a Manhattan plot. This approach has the advantage over standard forest plots that several outcomes can be integrated and shown in one figure.

Only 14 trials reported outcomes that are critical or important when considering whether to apply adhesion barriers—reoperation for adhesive small bowel obstruction, total incidence of adhesions, operation time of reoperation, and small bowel obstruction (any cause). Implementation of these outcome measures is one of the biggest challenges in the design of trials of new adhesion barriers.(65) Completion of future trials will be challenging because of the need for many patients to assess clinically critical outcomes, multicausality of some outcomes (eg, pregnancy rate), and to provide long-term follow-up data (eg, for adhesive small bowel obstruction). The risk of publication bias cannot be fully excluded—we identified some trials that have not been published yet. However, we do not believe that results of these trials will alter conclusions: the results of unpublished studies matched those of published reports and funnel plots showed no publication bias. Most of the trials were sponsored by

industry, which might have resulted in publication bias of positive results and overestimation of intervention effects. However, this effect seems unlikely because data of investigator-driven trials compare favourably with industry-sponsored trials and risk of publication bias was low.

Although serious adverse events were reported for half the trials, safety data for some barriers are scarce. Few adverse events were reported for oxidised regenerated cellulose, probably because the barrier was only studied in gynaecological surgery, in which little bleeding occurs. Previous studies showed that oxidised regenerated cellulose barriers cause an inflammatory response when in contact with blood.(66;67) Additional safety information for icodextrin comes from a large registry including over 4000 patients who had general and gynaecological surgery.(68;69) The data support the good safety profile of icodextrin.

Three Cochrane reviews have addressed adhesion prevention for gynaecological and open colorectal surgery.(14-16) The present study aggregates the evidence from these three reviews and includes additional evidence from trials of gastric and hepatic surgery as well as two trials of colorectal surgery that were missed by previous reviews.(43;55) Additionally, previous reviews did not rank different outcomes, despite the variety of consequences from a patient's perspective, and thus—for example—hiding the specific effect on adhesion incidence and type of small bowel obstruction.(14) An adhesion barrier cannot reduce the incidence of bowel obstruction secondary to tumour or hernia. In addition, we deemed operation time to be an important clinical outcome because evidence suggests that prolonged adhesiolysis increases the risk of inadvertent organ injury.(5;56) Compared with previous reviews, we did a more comprehensive and clinically meaningful analysis, which included risk of bias, risk of random error, a grey literature search, and an analysis of the role of sponsorship. The error matrix approach provides more detailed and clearer evidence of benefit and harm of an intervention. As more studies are done, clinical evidence increases and becomes more difficult to overview. The Manhattan plot helps to judge the relevance and strength of the evidence available for each specific adhesion-related outcome for a single intervention.

Oxidised regenerated cellulose reduces adhesion formation in fertility surgery. The implications for clinical practice remain unclear because none of the trials assessed pregnancy rate. With regard to the robustness of data for prevention of adhesion formation and safety, future studies should assess whether oxidised regenerated cellulose reduces reoperation-associated complications.

Hyaluronate carboxymethylcellulose reduces operation time in two-stage liver surgery and has a modest reduction effect on adhesive small bowel obstruction. The number needed to treat to prevent one case of adhesive small bowel obstruction is high for this rare but potentially life-threatening complication of general and gynaecological surgery. However, routine use in high-risk surgeries for bowel obstruction is warranted on the basis of our efficacy and safety results. We expect that with increasing evidence on clinical and socioeconomic effect of adhesiolysis, the use of hyaluronate carboxymethylcellulose to prevent organ injury during repeated open surgery will spread.(5;56)

Indications for the use of an adhesion barrier also depend on its formulation. Both oxidised regenerated cellulose and hyaluronate carboxymethylcellulose are solid barrier films and difficult to apply during laparoscopic surgery. Icodextrin and polyethylene glycol are easier to apply at laparoscopy. Formulation could also affect efficacy and adverse events. The solid and viscous gel barriers are thought to be more effective at preventing adhesion at sites of severe peritoneal injury and adhesiolysis, whereas liquid barriers provide better protection for injured surfaces—eg, by retractors or desiccation—distant from the region of surgical dissection. However, no clear evidence supports this hypothesis. Two adhesion barrier gels based on hyaluronic acid were associated with serious adverse events.19 We doubt whether the gel formulation contributed to these adverse events because the hyaluronate

carboxymethylcellulose film also becomes gelatinous after application. More likely, chemical adjuvants—the ferric ions—increase adverse tissue reactions.(70)

Results from our study could be used to develop guidelines for the use of barriers to prevent adhesion-related complications. Thus far, guidelines are only available for gynaecological surgery.(71)

Acknowledgments

We thank Patrica G Anderson for reviewing the report contextually and grammatically.

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Part III: Adhesion prevention

Chapter 11: Efficacy of polyethylene glycol adhesion barrier after gynaecological laparoscopic surgery: Results of a randomized controlled pilot study

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Published in: Gynecological Surgery. 2012; 9: 29-35

Abstract
Postoperative adhesions are the most frequent complication of peritoneal surgery, causing small bowel obstruction, female infertility and chronic pain. This pilot study assessed the efficacy of a sprayable polyethylene glycol (PEG) barrier in the prevention of de novo adhesions. 16 patients undergoing laparoscopic gynecological surgery were randomly assigned by shuffled sealed envelopes to receive either the adhesion barrier or no adhesion prevention. Incidence and severity of adhesions were scored at eight sites in the pelvis and reassessed by second look laparoscopy. Adhesion prevention was considered successful if no de novo adhesion were found at second look laparoscopy. One patient was excluded before randomization. Nine patients were randomized to treatment and six patients to control group. De novo adhesions were found in 0/9 patients who received the PEG barrier compared to 4/6 without adhesion prevention (0% vs. 67%, P = 0.01). Reduction in adhesion score was significantly greater in patients receiving PEG barrier (−2.6 vs. −0.06, P = 0.03). Meta-analysis of three randomized trials demonstrated that PEG barrier reduces the incidence of adhesions (odds ratio [OR] = 0.27; 95% CI 0.11–0.67). From this study, PEG barrier seems effective in reducing postoperative formation of de novo adhesions.

Background

Adhesions develop after gynaecological surgery in the pelvic cavity in almost all cases and cause significant morbidity .(1) In a large population-based study of gynaecological pelvic surgery, the readmission rate directly or probably related to adhesions was 13.9%, and the introduction of less invasive techniques, such as laparoscopy, did not seem to reduce this adhesion related morbidity.(2) The incidence of adhesive small bowel obstruction (ASBO) after oncologic gynaecological surgery is about 11%.(3) Adhesions are the leading cause of secondary female infertility worldwide, and an important cause of chronic pelvic pain.(4-7) In addition, adhesiolysis during reoperation is time-consuming and exposes the patient to the risk of unintended injury such as enterotomy.(1;8)

Adhesion barriers or anti-adhesive agents are needed because refinements in surgical techniques do not seem to be sufficient in reducing adhesion-related morbidity. Several products have come to the market ranging from membranes for selective coverage of injured peritoneal areas to liquids for broad nonspecific coverage. An important drawback of the available membranous adhesions barriers is the difficulty of handling them during laparoscopic procedures. Alternatives to membranes for laparoscopic use are sprays that are easily applied intraperitoneally through trocars at sites that need to be covered. Recently, a sprayable polyethylene glycol (PEG) anti-adhesion barrier was developed for anti-adhesive purposes (SprayGel; Confluent Surgical Inc., Waltham, MA). The PEG adhesion barrier consists of two liquid precursor solutions that quickly react to form a hydrogel after being sprayed and mixed in the abdomen. One of the precursors contains a small concentration of methylene blue allowing visualization of the area covered and the thickness of the hydrogel layer during laparoscopy. The hydrogel is biodegradable and physically separates the injured peritoneal sites in order to promote adhesion free peritoneal regeneration.

The PEG anti-adhesion spray proved to be effective in rodent and porcine models with 75% reduction of the incidence of adhesions in a rat cecal abrasion model and 60% reduction in a porcine uterine horn model.(9;10) Four human randomized controlled trials (RCTs) have been performed: two in patients undergoing laparoscopic or open myomectomy and two in patients undergoing loop ileostomy closure.(11-14) No RCT has included patients undergoing laparoscopic surgery alone, and all RCTs included a specific group of patients rather than investigating the various common types of laparoscopic benign gynaecological surgery. The use of PEG spray was correlated with a reduction in extend and tenacity of adhesions in these RCTs. However, reductions in adhesion incidence — in contrast to reduction in adhesion extend or tenacity — is particularly important for predicting the value of an anti-adhesive product reducing ASBO and unintended organ injury during adhesiolysis. We undertook a small prospective randomized controlled study to evaluate the PEG spray on adhesion formation in women undergoing common laparoscopic gynaecological procedures. In addition, we performed a meta-analysis of reported studies, including the present one, focusing on the efficacy of PEG spray in reducing the incidence of adhesions.

Materials and methods

The study was a randomized single-blinded (patient) study. Patients who were scheduled for laparoscopic treatment of benign gynaecologic disease involving ovaries, pelvic sidewalls, fallopian tubes or uterus were assessed for eligibility between September 2002 and March

2004. Inclusion criteria were as follows: age ≥18 years; the patient might benefit from and agrees to return for second look laparoscopy (SLL); and the patient agrees to use contraception until SLL was conducted.

Pregnant and lactating patients were excluded, as well as patients with known or suspected malignancy. Peroperative exclusion criteria were endometriosis classified as stage IV, using the Revised American Society for Reproductive Medicine Classification of Endometriosis scoring system and if complete adhesiolysis was not possible.(15)

At the end of index laparoscopic surgery and before removal of all instruments, patients were randomly assigned — via shuffled sealed envelopes — to treatment with PEG or no treatment groups. The PEG barrier was sprayed at all sites of surgical injury with the potential for adhesion formation. SLL was planned to evaluate adhesion formation. The surgeon performing SLL was blinded for the treatment group.

The study protocol was approved by the local Medical Ethical Committee and designed according to the ethical considerations described in the revised version of the Declaration of Helsinki (October 2008, Seoul). All patients gave written informed consent. The study was investigator-driven. PEG was kindly donated by Confluent, Surgical Inc (Waltham, MA, USA). The trial was registered at clinical trials.gov with identifier: NCT01187680.

Adhesion scoring

The incidence of patients with and without any adhesion was assessed in both initial and second look laparoscopies. All surgical procedures were performed by the same surgeons (EB and HV). Adhesions at SLL were classified as de novo adhesions or reformed adhesions. De novo adhesions are adhesions that are newly formed following the first laparoscopy at sites without any former adhesions. Reformed adhesions are adhesions that formed at the sites of adhesiolysis during the first laparoscopy.(16)

Adhesions were graded using the Local Adhesion Barrier Scoring System (LABS) score, based on the modified version of the American Fertility Society score system.(17) The LABS is an integrated score system comprising the adhesion's morphology and extend of the site covered with adhesions (Table 1). The LABS score differs from the modified version of the American Fertility Society score system; adhesions are scored at a lower number of sites that are more specific to gynaecologic surgery. Adhesions were systematically evaluated for incidence and LABS score at eight sites: both left and right tubes, ovaries and pelvic sidewall and the anterior and posterior uterus. For each patient, the total LABS score was calculated as the mean of LABS scores at these eight separate locations.

Table 1 Local Adhesion Barrier Scoring (LABS) system

LABS adhesion score		
Tenacity	**Extend**	**Score**
None	None (0% covered)	0
Mild	Localized (<33% covered))	1
Mild	Moderate (33%- 67% covered)	2
Mild	Extensive (>67% covered)	4
Severe	Localized (<33% covered))	4
Severe	Moderate (33%- 67% covered)	8
Severe	Extensive (>67% covered)	16

Safety aspects

All patients were treated in day care. Postoperatively, patients were controlled for temperature, pain, hemodynamic changes and signs of bleeding in the recovery area.

Outcomes

The primary outcome for this pilot study was the number of patients with de novo adhesions. Secondary outcomes were change in the number of sites covered with adhesions and change in LABS adhesion score.

The number of patients with any adhesions is the most preferable outcome of adhesion prevention studies. However, as the sample size of this pilot study would be inadequate to provide in sufficient power on this outcome, we addressed this outcome in meta-analysis of systematically searched studies on PEG adhesion barrier.

Power analysis

Based on animal studies, the incidence of de novo adhesions was estimated at 30% in the PEG group and 90% in the control group.(10) Fourteen patients in each arm of the study were needed to detect such difference with 80% power and 5% two-tailed significance threshold at 1:1 randomization. Accounting for loss to follow-up, a minimum of 30 patients were to be randomized.

Statistical analysis

All statistical tests performed were two-tailed with significance was determined at the 5% level. Unpaired t-test was used for the testing of continuous data and Fisher's exact test for dichotomous data. All statistical analyses were performed using SPSS 16.0.2 (SPSS inc., Chicago, ILL).

Meta-analysis

A comprehensive search of Pubmed and Embase search was performed on July 1, 2011 to identify papers published in peer-reviewed journals from RCTs in surgical or gynaecological patients for the intervention with PEG and outcome adhesions. In Pubmed, randomized trials were identified via the Cochrane Highly Sensitive Search Strategy for identifying randomized trials (sensitivity- and precision-maximizing version).(18) We selected randomized trials in Embase using the top performing search strategy (minimizing difference between sensitivity and specificity version) described by Wong et al.(19) Relevant RCTs were searched for data on the number of patients with any adhesions. The incidence of adhesions was expressed in odds ratio (OR) for meta-analysis. A fixed-effects model was applied for meta-analysis. In the presence of significant heterogeneity, the random-effects model was applied. Heterogeneity was tested with Cochrane Q-test and I2 test. An I2 value $\geq$50% or P value $<$0.05 was considered significant. Meta- analysis was carried out using Review Manager 5.0 (The Cochrane Collaboration, Copenhagen, Denmark).

End of study

The study was prematurely ended due to financial and organizational reasons. During the conduct of the study, the clinical trial insurance unexpectedly required a separate fee for both laparoscopic procedures in each patient.

Results

A total of 16 eligible patients gave informed consent. Fifteen underwent successful laparoscopic gynaecological or fertility surgery and were randomized. One patient had severe pelvic adhesions that could not be lysed completely and was excluded before randomization. There were no significant differences between the PEG and control group at index laparoscopy in age, type of surgical procedure, history of prior surgery, Chlamydia serology and smoking status at baseline (Table 2). Adhesiolysis was performed in 14 patients.

Table 2 Baseline characteristics

	PEG	**Control**	**P value**
Number of randomized patients	9	6	
Age	30.1±5.7[a]	34.5±4.3[a]	0.12
Type of surgerical procedures performed			
Adhesiolysis	8 (89%)	5 (83%)	>0.99
Salpingotomy/ Salpingectomy	4 (44%)	2 (33%)	>0.99
Cystectomy	2 (22%)	3 (50%)	0.33
Prior surgery			
* Laparotomy	0/9 (0%)	0/6 (0%)	>0.99
* Laparoscopy	5/9 (56%)	5/6 (83%)	0.58
Positive chlamydia serology	4/9 (44%)	1/6(17%)	0.58
Smoker	1/9 (11%)	0/6 (0%)	>0.99
Completed SLL	9 (100%)	6 (100%)	>0.99

[a]= Mean ± SD

At index laparoscopy, there was a non-significant trend towards more sites covered with adhesions (5.1 ± 2.3 vs. 3 ± 2.2; P = 0.10) and higher LABS score (3.7 ± 2.8 vs. 2.4 ± 3.0; P = 0.40) in the PEG group (Table 3). Time of surgery was comparable between the PEG and control group at index laparoscopy. Time period between initial and second look laparoscopies was similar for both groups: 27.9 ± 11.5 days in the PEG group and 28.0 ± 17.6 in the control group (P > 0.99).

All 15 randomized patients underwent SLL. De novo adhesions were found in 0/9 patients in the PEG group (0%) compared to 4/6 (67%) of patients in the control group (P = 0.01). Patients in the PEG group had a decrease in LABS score compared to an increase in the control group (−2.6 ± 2.1 vs. 0.1 ± 1.7; P = 0.03). This decrease was most prominent at the ovaries and fallopian tubes sites. The change in the number of sites covered with adhesions was −2.4±2.0 for patients treated with PEG spray compared to 0.8 ± 2.3 for control patients (P = 0.01). There were no significant differences in the absolute incidence, sites covered with

adhesions and LABS scores between the PEG group and controls at SLL (Table 4). There were no post- operative complications in both groups.

Table 3 Adhesions at initial laparoscopy

	PEG	**Control**	**P value**
Patients with any adhesion	8/9 (89%)	5/6 (83%)	>0.99
Adhesion sites	5.1±2.3[a]	3±2.2[a]	0.10
LABS- score (Mean)	3.7±2.8[a]	2.4±3.0[a]	0.44
• Left Ovary	5.1±4.9	2.0±3.3	0.17
• Right Ovary	5.8±6.0	4.0±6.2	0.59
• Left Fallopian Tube	6.4±5.8	2.0±3.3	0.08
• Right Fallopian Tube	6.2±5.7	3.5+6.3	0.42
• Left Pelvic Side Wall	3.3±3.2	1.3±3.3	0.27
• Right Pelvic Side Wall	1.6±2.8	4.3±6.5	0.36
• Anterior Uterus	0.2±0.7	0.0±0.0	0.35
• Posterior Uterus	1.2±1.7	2.7±2.1	0.19
Time of surgery (min)	151.9±29.5[a]	146.7±47.8[a]	0.82
Time to SLL* (days)	27.9±11.5 [a]	28.0±17.6[a]	>0.99

* SLL = second look laparscopy
[a]= Mean ± SD

Although no significant differences were found in the incidence of adhesions at any of the specific sites at SLL, the effect of PEG appeared maximal at the ovaries. The incidence of adhesions around the ovaries was reduced between index laparoscopy and SLL in the PEG treated group by 33% and 44% for the right and left ovaries, respectively. On the contrary, a 17% and 33% increase in incidence of adhesions around the right and left ovaries, respectively, was seen in control patients.

Meta-analysis of adhesion incidence

A total of 85 papers from peer-reviewed journals were identified using the search strategy. Five papers were identified studying the efficacy of PEG on adhesion formation after peritoneal surgery in an RCT.(11-14;20) The number of patients with any adhesions could be assessed from three papers investigating patients undergoing myomectomy.(11;13;20) One paper was excluded because it described an interim analysis and results from the completed study were described in another paper.(11;20) Thus, two RCTs and the present study remained for meta-analysis. In all here studies a trend towards a lower overall incidence of adhesions was demonstrated in PEG treated patients. Pooled data, using a fixed effects model, showed a significant reduction of the incidence of adhesions with an OR of 0.27 (95% CI 0.11–0.67; P = 0.005, Fig 1).

Table 4 Adhesions at second look laparoscopy

Outcome:	PEG	Control	P- Value
Patients with any adhesion	7/9 (78%)	6/6 (100%)	0.49
Patients with *de novo* adhesions	0/9 (0%)	4/6 (67%)	0.01
Adhesions (number of sites)	2.7 ± 2.4[a]	3.8 ± 1.7[a]	0.29
Δ Adhesions (number of sites)*	-2.4 ± 2.0[a]	0.8 ± 2.3[a]	0.01
LABS- score (Mean)	1.2±1.3[a]	2.4±2.4[a]	0.29
• Left Ovary	0.7±0.9	2.2±3.0	0.28
• Right Ovary	2.9±5.2	5.5±6.4	0.43
• Left Fallopian Tube	2.2±3.3	1.7±1.4	0.66
• Right Fallopian Tube	2.3±2.8	2.8±6.5	0.86
• Left Pelvic Side Wall	1.0±2.6	0.7±1.0	0.74
• Right Pelvic Side Wall	0.0±0.0	4.0±6.7	0.20
• Anterior Uterus	0.0±0.0	0.0±0.0	1.00
• Posterior Uterus	0.3±0.5	2.5±3.1	0.15
Δ LABS- scoreb (Mean)	-2.6±2.1[a]	0.1±1.7[a]	0.03
• Left Ovary	-4.4±5.1	0.2±2.2	0.03
• Right Ovary	-2.9±4.8	1.5±5.3	0.13
• Left Fallopian Tube	-4.2±5.0	-0.3±4.0	0.12
• Right Fallopian Tube	-3.9±4.0	-0.7±1.2	0.05
• Left Pelvic Side Wall	-2.3±2.8	-0.7±3.7	0.38
• Right Pelvic Side Wall	-1.6±2.8	-0.3±0.8	0.24
• Anterior Uterus	-0.2±0.7	0.0±0.0	0.35
• Posterior Uterus	-0.9±1.5	-0.2±2.7	0.57

[a]= Mean ± SD

bΔ= difference between index laparoscopy and second look laparoscopy

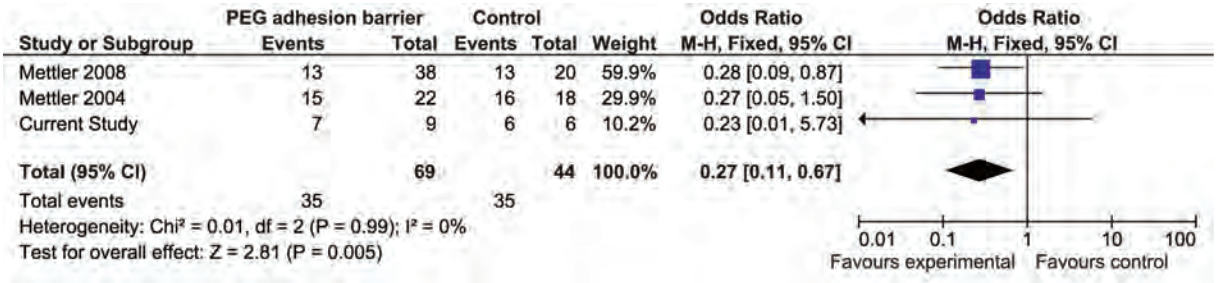

Figure 1 Results from meta-analysis on the efficacy of PEG adhesion barrier reducing the total incidence of adhesions

Discussion and conclusion

From this study, PEG anti-adhesion barrier seems effective in the prevention of de novo adhesions in common gynaecological laparoscopic procedures, but especially in fertility enhancing procedures. Furthermore, there was a significant difference in change of LABS score favouring patients treated with PEG adhesion barrier. Meta-analysis also showed a significant reduction in the total incidence of adhesions.

The PEG anti-adhesion barrier has a set of unique characteristics compared to other existing barriers. The formula of two liquid PEG precursors that rapidly polymerize into a solid hydrogel, allows the surgeon to laparoscopically apply a barrier with the characteristics of a site specific barrier and the ease of application of a liquid.(12) Most site specific barriers are solid membranes that are difficult to apply laparoscopically. Site specific adhesion barriers seem most efficacious against adhesion (re)formation as they remain on the exact place of application during mesothelial healing. In the study of Ferland et al. both uterine horns and opposing peritoneum in a porcine model were abraded. One side was randomly assigned to coverage with a 1- to 2-mm-thick layer of PEG adhesion barrier. The barrier remained in place, and at SLL a significantly lower incidence of adhesion was found at the treated sides, demonstrating that the PEG adhesion barrier acts as a site-specific adhesion barrier.(10) The methylene blue dye makes it easy to assess if an area is sufficiently covered with the PEG anti-adhesion barrier. PEG molecules polymerize without the need of an external energy source or excess heat production and the hydrogel remains intact for 5–6 days, which is long enough for peritoneal layers to heal.(21) When degrading, the hydrogel falls apart in water-soluble PEG molecules that are easily resorbed and cleared in the urine.(22)

Although a small number of patients could be included in this trial, our findings support those of earlier studies demonstrating that PEG spray is a highly efficacious site specific barrier for laparoscopic use. The incidence of adhesions could be assessed from two previous RCTs in patients undergoing myomectomy.(11;13) In the present study and the two RCTs, a trend towards a lower overall incidence of adhesions was demonstrated in PEG treated patients. Pooled data showed a significant reduction of the incidence of adhesions in our meta-analysis. Complete adhesion prevention is of particular importance as it is the only means of providing a definitive protection against all adhesion related complications, such as infertility, ASBO and inadvertent enterotomies.

A limitation of this study is the analysis of adhesion prevention and not the clinical complications of adhesions, such as infertility or ASBO. Infertility as an endpoint is difficult to assess because failure to attain pregnancy is a multi-factorial endpoint. To assess the efficacy of adhesion barriers on fertility, a randomised trial is required in subfertile patients due to tubal pathology, which compares use of a barrier to no treatment after adhesiolysis and compares time to natural conception. Oxidized regenerating cellulose (Interceed®, Ethicon, Sommerville, NJ) is the only adhesion barrier that was proven to increase pregnancy rate in an RCT.(23) However, oxidized regenerating cellulose has limitations because it is difficult to handle laparoscopically and can cause adverse adhesiogenic effects in the presence of blood.(24;25) Studies evaluating the efficacy of adhesion barriers in reducing the number of ASBO and enterotomies are rare. The incidence of these complications is relative low, thus a large number of patients is needed to demonstrate a significant effect. Modified sodium hyaluronic acid (HA) and carboxymethylcellulose (Seprafilm®; Genzyme Corporation,

Cambridge, MA) reduced the number of ASBO requiring reoperation or found at autopsy by 45% in a study of 1,701 patients who underwent benign colorectal surgery.(26) This barrier has limitations because it cannot easily be applied at laparoscopy.

Change in adhesion score can be difficult to interpret as an outcome measure for adhesion prevention because the adhesion score at baseline influences the maximal effect. However, in our study, not only the size but also the direction of the effect differed between the groups. There was a marked decrease in LABS adhesion score in PEG treated group, while patients in the control group had a slight increase in adhesion score.

To study the efficacy of adhesion barriers by means of a second look procedure is becoming increasingly difficult. First, it is deemed more and more unethical to perform an invasive second procedure just for scientific purposes. Second, the benefit of SLL as part of fertility surgery is questionable. Today, women have more access to alternative treatment modalities to become pregnant such as in vitro fertilization.(27) Future adhesion prevention studies expectedly have to rely on non-invasive techniques to evaluate adhesion formation. For long, this has been considered impossible but recent studies show promising results of cine-MRI as a non-invasive diagnostic tool for the detection of adhesions.(28) More experience is needed to delineate the value of cine-MRI as an alternative to SLL in adhesion prevention studies.

Sprayable barriers that can be introduced via a laparoscopic trocar and handled with ease in the abdominal-pelvic cavity are of surplus value in the therapeutic arsenal of adhesion preventive agents. Clinical trials have demonstrated that laparoscopy only reduces the extend of adhesions but does not decrease the incidence of adhesions.(29;30) Maximal efforts to prevent adhesion formation in fertility surgery should therefore comprise laparoscopy as well as an adhesion barrier. Although a large number of agents show adhesion reduction in animal models, only a few demonstrated such effects in RCT in humans.(31/33) PEG is one of a few barriers that has been evaluated in both gynaecological and gastrointestinal patients and was found to be effective in both our study and previous RCTs.(11;13;14;20) However, more research is needed to investigate the effect on adhesion related complications, such as ASBO and infertility.

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General discussion and agenda for the future

Epidemiology and prevention of postsurgical adhesions revisited

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Abstract
Since the landmark SCAR studies elucidated the impact of adhesions on readmissions for long-term complications of abdominal surgery, adhesions are widely recognized as one of the most common causes for complications following abdominal surgery. Concurrently, interest in adhesion prevention revived and several new adhesion barriers were developed. Although these barriers have now been around for more than a decade, adhesion prevention is still seldom applied. The main reasons why adhesion prevention is not applied seem a continuing lack of awareness of the burden of adhesion related complications, questions on the indications and cost-efficacy of adhesion barriers, and safety concerns. New epidemiologic data warrant a paradigm shift in our understanding of the socioeconomic burden of adhesion related complications and the indications for adhesion prevention strategies. Increasing evidence from cohort studies and systematic reviews show that difficulties during reoperations, rather than small bowel obstructions, account for the majority of adhesion related morbidity. New cost-efficacy models that include the potential benefits of adhesion prevention in reoperations and fertility treatments are expected to indicate that prevention is also cost-effective in high risk surgeries, and will be applicable to a broader group of patients. More effort should be put into improvement of research on adhesion prevention from molecule to man to population. Animal models need to be better standardized and powered to generate more meaningful and robust results. There is a need for non- invasive techniques to assess adhesion formation in clinical trials. Cine-MRI holds promise, but needs further development.

INTRODUCTION

The SCAR group's 1991 landmark study strongly suggested, based on hospital admission data, that adhesion formation is the most common cause of long-term complications after abdominal surgery. Concurrently, interest in adhesion prevention revived, and the biomedical industry developed several barriers to prevent adhesion formation.(1-3) The new barriers which came to the market consistently reduced the incidence of post-surgical adhesions in randomized trials.(4-6) However, these findings have not led to broad and routine use of adhesion barriers in general, urological, or gynaecological surgery.

The main reason why adhesion prevention is not widely practiced seems to be a lack of awareness regarding the burden adhesions place on patients and society. Less than 10% of surgeons and gynaecologists routinely inform their patients about the risks of adhesions during informed consent.(7;8) Surgeons and gynaecologists also underestimate the number of hospital readmissions related to adhesions, as well as the incidences of adhesion-related bowel obstructions, and infertility following abdominal operations.(7;9) The consequences and complications of adhesions during reoperations are especially underexposed in the literature. Despite the growing evidence that the disease burden related to adhesiolysis and bowel injuries made during reoperations might exceed that of adhesive small bowel obstruction in terms of incidence and socioeconomic costs.(10;11)

The second reason underlying reluctant use of anti-adhesion barriers is that many questions remain regarding adhesion prevention strategies in general and adhesion barriers in particular. Despite previous Cochrane reviews showing a potential reduction of postoperative adhesion formation, surgeons question if adhesion barriers are effective at reducing adhesive small bowel obstruction and adhesion-related infertility, or if the 'effect size' is large enough for routine application. (7;9;12;13) Some believe that adhesion barriers might actually harm patients because single bands of adhesions resulting from incomplete adhesion prevention put a patient at greater risk for strangulated bowel obstruction than multiple matted adhesions do. Such concerns persist despite epidemiological studies which have refuted these arguments.(14;15) Aside from safety concerns, medical professionals and policy makers both question the cost- effectiveness of adhesion barriers. Finally, many physicians question the need for adhesion prevention in the era of minimally invasive abdominal surgery.

Taken together, these questions and arguments warrant revisiting the epidemiologic evidence concerning adhesion formation and prevention. In this article, we discuss up-to-date evidence on the morbidity of adhesions, and comprehensively assess the impact of surgical techniques and adhesions barriers on adhesion formation and clinical endpoints. Further, we provide directives for future studies to improve patient outcomes regarding adhesions.

ADHESION BURDEN

Unlike other postoperative complications such as wound infection or anastomotic leakage, adhesion formation places patients at lifelong risk for various clinical disorders. These complications include small bowel obstruction, female infertility, difficulties during reoperations, and chronic pain.(15)

SBO as an outcome of adhesion-related morbidity

Most studies of adhesion-related morbidity focus on adhesive small bowel obstruction (SBO) (Figure 1).(15) Although adhesive SBO is relatively rare, it inflicts considerable harm on those impacted, resulting in eight days of hospitalization on average, and an in-hospital mortality rate of 3% per episode.(16-19) The risk of SBO is highest following colorectal and oncologic gynaecological surgery.(2;3;15;20) The overall incidence of bowel obstruction following abdominal surgery is estimated at 9%, with adhesions being the single most common cause of obstruction (56% of cases).(15)Recurrence of SBO is also considerable; 12% of conservatively treated patients are readmitted within one year, rising to 20% after five years. The risk of recurrence is slightly lower after operative treatment, at 8% after one year and 16% after five years.(21)

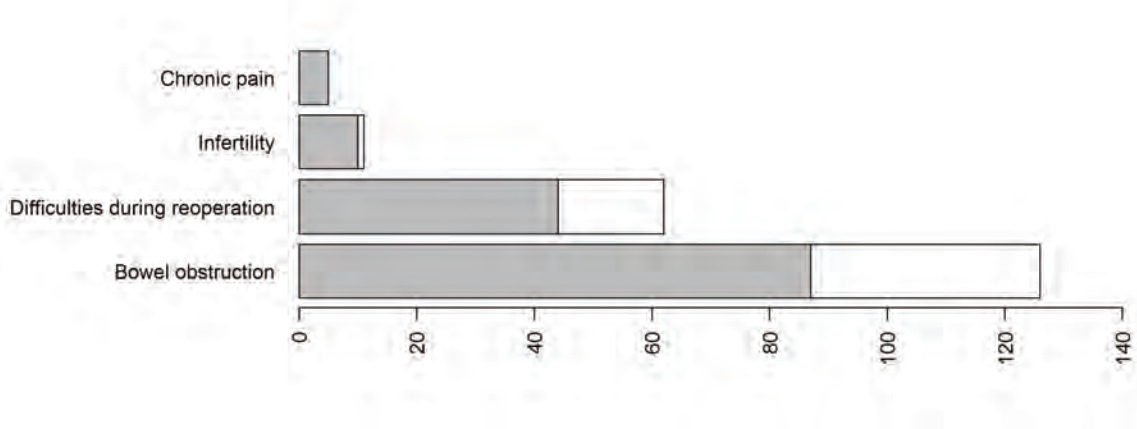


Figure 1 Number of included articles in a recent systematic review on adhesion-related morbidity, sorted by type of adhesion-related complication, covering articles published in past two decades.

Dark= Articles publishing data on adhesion-related morbidity as a primary or main secondary outcome
light= Articles publishing data on adhesion=related morbidity as a additional outcome
Derived from: ten Broek RP, Issa Y, van Santbrink EJ et al. Burden of adhesions in abdominal and pelvic surgery: systematic review and met-analysis BMJ 2013;347:f5588

Sikirica et al. estimated in-hospital annual costs of adhesions in the United States to be $2.3 billion, comparable to the total medical costs of peptic ulcer disease and eclipsing the in-hospital costs of rheumatoid arthritis.(22-24) Costs associated with the treatment of an adhesive small bowel obstruction are estimated to be $3,000 per episode with conservative treatment and $10,000 with operative treatment.(25;26) The additional costs incurred by operative treatment are partially due to complications of adhesiolysis. The incidence of bowel injuries during adhesiolysis for SBO is estimated to be between 6% and 20%.(27-29)

Adhesiolysis complications as an outcome of adhesion-related morbidity

Bleeding, trocar injury, conversion from laparoscopy to laparotomy, and damage to peritoneal organs such as the bowel, liver, spleen, bladder, and ureter are well-known operative complications of adhesiolysis. Epidemiological data on these complications,

however, are relatively scarce. Our group was the first to comprehensively study the incidence of inadvertent enterotomy in reoperations. A retrospective analysis of 270 reoperations revealed an unintended enterotomy in nearly 20% of patients.(10) More recently, we demonstrated in a large prospective cohort study that adhesiolysis requires a median of 20 minutes of operative time and is associated with a 10% risk of iatrogenic bowel injury.(11) This fifty percent difference between studies is explained by the different case mix of abdominal procedures in each study, and by the decision not to count perforations close to pre-existing bowel fistulas in the prospective analysis.

Although bowel injury is relatively rare in gynaecological laparoscopies, one study reported an 11% incidence of bowel injuries during gynaecological laparoscopy following major open gynaecological or general surgery.(30) In a subgroup of our prospective LAPAD (LAParotomy or LAParoscopy and ADhesiolysis) study population, median adhesiolysis time was 11 minutes (range 0- 177 minutes) in 103 patients with a history of gynaecological operations, while the incidence of bowel injury was 11%. Most of these bowel injuries occurred in women who had undergone colorectal surgery (54.5%) or abdominal wall surgery (36.4%).

In a second study, we demonstrated that the number of previous laparotomies, the anatomical site of operation (lower gastrointestinal tract and abdominal wall), the presence of bowel fistulas, and an incision through a pre-existing scar were independent risk factors for bowel injury.(31) A clinical scoring system and nomogram for the risk of bowel injuries was developed based on these four risk factors, with a 50% predicted risk of bowel injury when all four risk factors are present. The scoring system needs validation in an external cohort.

In repeat caesarean sections adhesiolysis increases the risk of bladder injury six-fold compared to primary sections.(32) Moreover, when compared to primary caesarean section, delivery of the infant was delayed by about six minutes during repeat caesarean sections, and its one-minute Apgar score was significantly lower.(33)

Performing adhesiolysis results in significant postoperative morbidity and mortality, both from bowel injuries and from other complications. Inadvertent enterotomies alone are associated with an in-hospital mortality rate of 8%. Bowel injuries aside, adhesiolysis also increases the risk of postoperative wound infections (6.5% vs. 2.5%), abscesses (2.7% vs. 0.7%) and sepsis (2.9% vs. 0.7%). The increase in direct hospital costs associated with adhesiolysis are estimated at $4,000 per operation, rising to almost $30,000 if a bowel injury occurs.(11)

Taken together, these recent epidemiological data on adhesiolysis morbidity and procedural costs indicate that adhesiolysis is comparable to one episode of SBO. The incidence of adhesiolysis, however, is much more frequent than SBO. Today, as many as 40%-66% of elective procedures in general surgery are reoperations.(6;11;34) This number is expected to rise as life expectancies increase and more advanced surgical and anesthesiological techniques emerge. Thus, adhesiolysis might actually be the largest adhesion-related complication in terms of morbidity and socioeconomic costs.

Secondary infertility as an outcome of adhesion-related morbidity

Adhesions of the fallopian tubes are a leading cause of acquired female infertility. Adhesions are found during diagnostic laparoscopy in approximately 20-40% of female

patients with infertility.(35;36) However, it is difficult to distinguish how many of these adhesions are postsurgical and how many are due to pelvic inflammatory disease or endometriosis. In a recent meta-analysis, we showed that fertile female patients undergoing proctocolectomy for inflammatory bowel disease have a significantly lower pregnancy rate compared to non-operated patients (OR 0.15; 95% CI: 0.08- 0.29).(15) In addition, as many as 20-30% of these previously operated patients sought fertility treatment.(37;38)

The most commonly used fertility treatments are reconstructive microsurgery with peritubal adhesiolysis and in vitro fertilization (IVF). The use of reconstructive microsurgery has declined over recent years in favour of IVF; however, reconstructive fertility treatment offers a number of potential benefits over IVF. Adhesiolysis is a curative treatment providing couples with unlimited attempts to conceive naturally. Costs of reconstructive surgery are also lower, and serious adverse events related to IVF such as ovarian hyperstimulation syndrome are avoided.(39)

The varying results of peritubal adhesiolysis are the driving force behind the declining use of reconstructive surgery in the treatment of adhesion-related infertility. Pregnancy rates ranging from 20% to 80% have been reported following peritubal adhesiolysis.(40-43) Pregnancy rates seem to be highest in patients with filmy adhesions, decreasing to 20% in patients with dense adhesions. The use of adhesion barriers may help to preserve fertility and improve peritubal adhesiolysis outcomes, although these outcomes have not yet been studied in a randomized trial. The cost-effectiveness of adhesion barriers in fertility surgery has also not been evaluated.(44)

Chronic pain as an outcome of adhesion-related morbidity

While adhesions and chronic pain often coincide following abdominal surgery, the causative role of adhesions in chronic pain is debated. In a trial randomizing between laparoscopic adhesiolysis and no treatment beyond pneumoperitoneum for chronic pain related to adhesions, both groups experienced long term pain relief. These findings further fed the debate.(45) In 2004 Demco et al. addressed the ongoing controversy concerning adhesions and pain in a series of pain mapping experiments.(46) They found that touching and moving adhesions elicited a clear pain sensation which was most prominent for filmy adhesions connected to mobile organs.(46) Disruption of painful filmy adhesions by pneumoperitoneum may explain the long term pain relief of control patients in the aforementioned trial. Recent long-term follow-up data from a trial randomizing between an adhesion barrier film and no specific adhesion prevention, showed a lower number of patients with chronic abdominal complaints in the adhesion barrier group.(47)

Paradigm shift regarding adhesion impact

The new epidemiological data on the burden of adhesiolysis during reoperations represent a paradigm shift in our understanding of adhesion-related morbidity and strategies for adhesion prevention (Table 1). Previous cost models for adhesion barriers that focused on prevention of SBO demonstrated that these agents might be cost- effective for selected patients.(25) However, since a drawback of attempting to prevent SBO is that obstruction can be caused by just a single adhesive band, prevention of SBO therefore requires total adhesion

prevention in the whole peritoneal cavity. This is relatively difficult to achieve without compromising safety of the barrier.

A more complete cost-effectiveness model would also account for the additional costs incurred by reoperations, fertility problems, and chronic visceral pain treatments. It is expected that such a complete model would reveal that barriers are cost-effective in most patients who undergo abdominal surgery because reduction of adhesion formation would already provide benefit.

The extent of difficulties encountered during reoperations correlate to the extent and severity of adhesion formation. Evidence shows that an increase in time needed to perform an adhesiolysis—a surrogate for the extent and severity of adhesions—is correlated with an increased risk for inadvertent bowel injury.(11;48) Thus, while optimization of surgical technique and use of adhesion-reducing agents may not completely prevent adhesion formation in operations with extensive peritoneal damage and subsequent risk of SBO, reducing the extent and severity of adhesions is likely to have a beneficial effect on the outcomes of future operations and on fertility. In a recent trial, the application of an adhesion barrier for two-stage liver surgery resulted in reduced operative times and a trend toward fewer complications from the second procedure.(49)

Table 1

Summary of current insights in adhesion-related morbidity
The incidence of postoperative bowel obstruction is 9% (7%-10%), depending on the type of operation. Most of these obstructions are caused by adhesions (56%; 49%-64%).
Adhesiolysis requires 20 minutes of operative time and is associated with a 10% risk of iatrogenic bowel injury. The additional direct hospital costs of adhesions are approximately $ 4,000.
Bowel injury results in 8% mortality and requires additional bowel resections and anastomosis in 60% of cases.
Pregnancy rates drop to 50% after proctocolectomy and result in high use of fertility treatments (20-30% of fertile-aged female patients).
Colorectal, abdominal wall, and oncological gynaecologic surgery yield the highest risk for adhesion-related complications.
What needs further investigation
Impact of adhesions on quality of life, indirect costs, return to work, etc.
Impact of adhesiolysis and subsequent complications on quality of oncological resections and adjuvant treatment.
Extent of adhesion formation after major laparoscopic surgery (e.g. laparoscopic colorectal surgery).
Burden of adhesions after peritoneal surgery in urology.

ADHESION PREVENTION

Surgical technique

The first step in preventing post-operative adhesions is minimization of injury to serosal surfaces and the parietal peritoneum. However, it is difficult to substantiate “good surgical technique”, and claims thereof are based primarily on personal preferences and experiences

rather than published data. Comparison of surgical techniques is also difficult to achieve in a randomized trial aside from laparoscopy versus open surgery.

We recently performed a systematic review and meta-analysis on the impact of different surgical techniques on adhesion formation.(50) There is some evidence that laparoscopy and not closing the peritoneum each have a beneficial effect on the incidence of adhesions. No effect could be demonstrated, however, for clinically important outcomes such as reoperations for bowel obstruction and pregnancy rate. In the SCAR studies, laparoscopy failed to demonstrate consistent beneficial effects on adhesion-related morbidity in gynaecological surgery, except for in the subgroup of minor surgical procedures.(3) Additionally, no beneficial effect was demonstrated in a three-year follow-up study of patients who were randomized to laparoscopic or open colorectal surgery.(51) However, a meta-analysis of non-randomized studies shows that laparoscopy in general does seem to have a slight lowering effect on the incidence of small bowel obstruction.(15)

From a pathophysiological point of view, minimally invasive techniques reduce the extent and severity of adhesion formation. Nonetheless, all peritoneal trauma has the potential to result in adhesion formation. In laparoscopy, the same amount of dissection needs to be performed as in open surgery, creating large peritoneal wound surfaces during colorectal and oncological surgery. This might explain why laparoscopy was only beneficial for adhesion-related outcomes after minor surgical procedures in the SCAR studies. Additionally, pneumoperitoneum itself may contribute to adhesion formation. In a series of experiments on the role of pneumoperitoneum on adhesion formation, the group from Leuven demonstrated that factors such as pressure and duration of pneumoperitoneum, mesothelial cell hypoxia (caused by the use of pure CO2), reactive oxygen species (pneumoperitoneum with more than 4% oxygen), desiccation, and mesothelial trauma all modulated local tissue response.(52) The local tissue response elicits release of inflammatory cytokines, growth factors, and enzymes such as matrix metalloproteases, TGF-beta1, TGF-beta3, tachykinins, and INF-gamma, all of which are known for their role in adhesion formation.(53-56) A key factor in the local tissue response is a decreased fibrinolysis capacity due to increased levels of plasminogen activator inhibitor activity(PAI) and decreased levels of tissue-type plasminogen activator (tPA), leading to permanent fibrinous attachments.(54)

Adhesion formation in laparoscopy might be reduced by conditioning the pneumoperitoneum.(52) In a human pilot study, Koninckx et al. demonstrated a significant reduction in the incidence of adhesions when the pneumoperitonuem was conditioned using a gas mixture of 86% CO2, 10% N2O, and 4% O2, combined with cooling and humidification of the gas with 2–3 ml/min of Ringer's lactate and 1,000 IU of Heparin/L.(57) Furthermore, the type of coagulation device might impact laparoscopic adhesion formation. An ultrasonic device, commonly used in laparoscopic procedures, produces less extensive damage than electrocautery.(58;59) Such factors seem to be of limited importance in short laparoscopic procedures with low complexity, but have considerable effects on the levels of tPA in prolonged laparoscopic procedures.(60;61)

In summary, despite benefits reported in experimental animal and clinical studies, laparoscopy does indeed induce adhesion formation. This evidence contradicts the general statement that an adhesion prevention agent is not necessary in laparoscopic surgery.(14;15;50;52)

Agents to prevent adhesion formation – the pre-clinical phase

Approximately 60 to 80 animal studies that investigate the efficacy of existing and newly-developed adhesion reducing agents are published annually (data not shown). The most commonly used models are the caecal abrasion, uterine horn, and ischemic button models. A commonality among these models is that a standardized lesion is made to the peritoneum, and adhesions are then scored seven to twenty-one days later after sacrificing the animals. Although these methods of studying adhesion formation and barrier efficacy may seem to be sufficient, animal models have many drawbacks, and translating results to clinical practice is cumbersome.

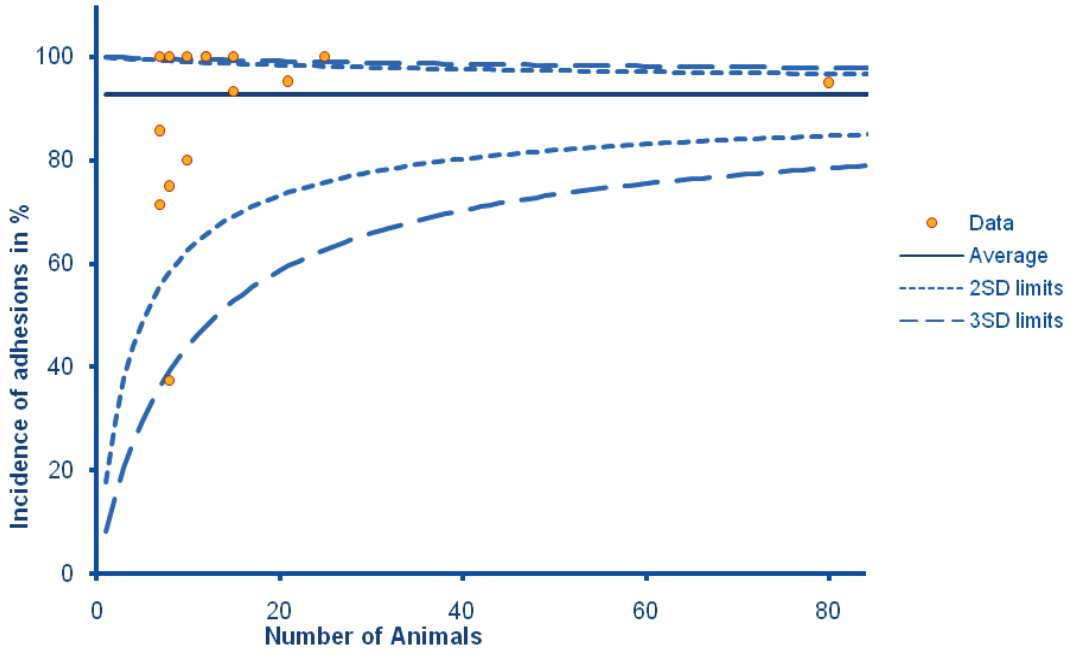
To highlight some of the drawbacks of these animal models, we evaluated thirteen studies investigating the efficacy of hyaluronate carboxymethylcellulose using a caecal abrasion model. When we compare the incidences of adhesions in these studies, a large variation is found in both control and experimental groups (Figure 2). Two methodological flaws contribute to this wide variation; the first is lack of standardization. There is (too) much variation, for example, in techniques used for abrasion and additional peritoneal lesions, day of sacrifice, methods of scoring adhesions, and research conditions. The second flaw is that most studies are not powered at all, or are powered to score characteristics of adhesions rather than the incidence of adhesions. Using an adhesion score might seem attractive because it reduces the sample size required to demonstrate differences between groups with sufficient power. However, such scores are highly subjective, and most models only induce relatively mild “de novo” adhesions which are not very challenging to prevent. Many patients, on the other hand, already have adhesions from prior surgery, making reformation after lysis more difficult to prevent. Another problem with translating the results of animal studies is the inability to investigate clinically relevant endpoints such as SBO and fertility. Reduction of adhesion score alone in an animal model, therefore, is by no means a guarantee of success in clinical studies. Indeed, many agents showing promising results in animal models have not shown significant effects in clinical studies.(12;13)

Agents to prevent adhesion formation – clinical application

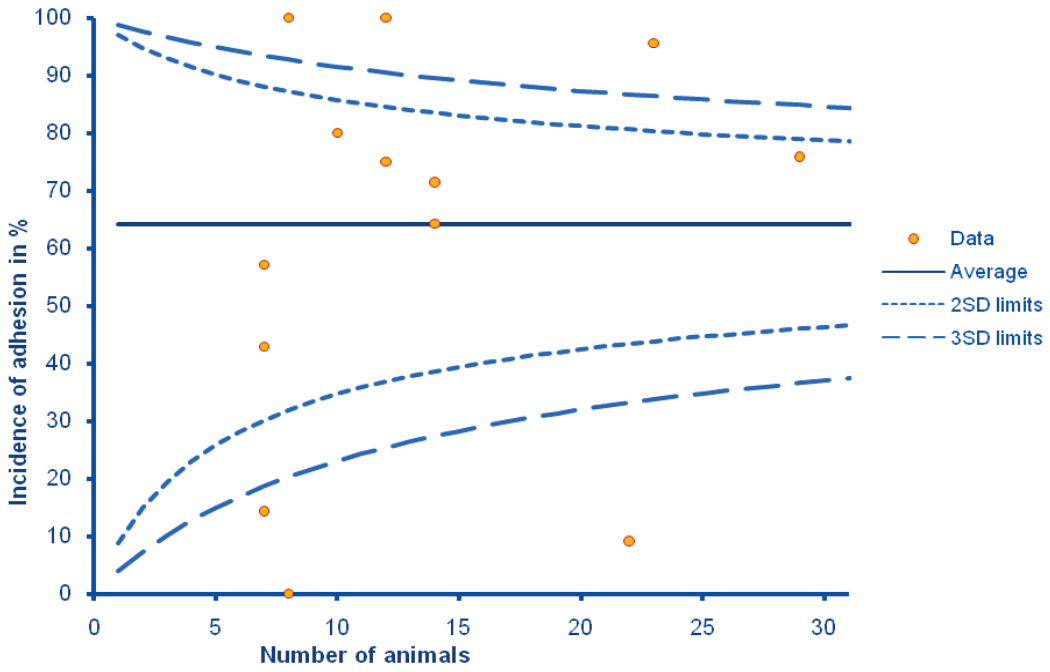
Available adhesion-reducing agents can be grossly divided into three groups: systemic pharmacological agents, intraperitoneal pharmaceuticals, and local adhesion barriers. Systemic agents targeting inflammatory response—mainly steroids—have been quickly abandoned, since the use of steroids did not result in reduced adhesion scores at second look surgery, nor was there a benefit on pregnancy rate in randomized trials.(62;63)On the contrary, serious side effects were reported with peri-operative use of steroids, including wound healing problems and suppression of the pituitary- adrenal axis.

One of the first agents applied as a local pharmaceutical to prevent adhesions in a clinical study was heparin, which proved unsuccessful.(12) Recombinant plasminogen activator (rPA) holds promise as a local acting adhesion formation-reducing agent. Plasminogen activator plays a key role in activating fibrinolysis. The innate human fibrinolytic response is often insufficient to prevent adhesion formation following peritoneal trauma.(64) Stimulating fibrinolytic activity with rPA in rodents reduces the incidence of both adhesion formation andperitoneal abscesses, and is safe for use in bowel anastomosis models.(65;66) Experience

with the use of rPA in humans is still limited to pilot and dose-finding gynaecological studies.(67)



A.



B.

Figure 4

A. Incidence of adhesions in control groups of animal studies for the efficacy of hyaluronate carboxymethylcellulose using cecal abrasion model

B. Incidence of adhesions in treatment groups of animal studies for the efficacy of hyaluronate carboxymethylcellulose using caecal abrasion model

Most of our clinical experience in adhesion prevention is with the use of adhesion barriers. Adhesion barriers are produced in several forms: solid membranes, gels, and liquids. The concept behind barriers is that they do not actively interact with inflammation and wound healing. Rather, they act as a spacer which separates injured surfaces of the peritoneum, allowing these surfaces to heal without forming fibrinous attachments which eventually lead to adhesions. In order to accomplish this task, such barriers should ideally be inert to the human immune system and be slowly degradable. Since the entire surface of the peritoneum quickly epithializes—unlike skin, which does so gradually from the borders— the time required for regeneration is approximately seven days irrespective of the size of the peritoneal injury.(56) Abdominal inflammation and other complications, however, might prolong peritoneal healing, thereby necessitating a barrier that is effective for more than a week.

Four adhesion barriers have been approved for clinical use by legislative authorities in the United States and Europe: hyaluronate carboxymethylcellulose (Seprafilm®, Sanofi, Paris, France), oxidized regenerated cellulose (Interceed®, Johnson & Johnson, New Jersey, NY, USA), icodextrin 4% solution (Adept®, Baxter, Deerfield, IL, USA), and polyethylene glycol (PEG) (Spraygel®, Sprayshield®, Confluent Surgical, Waltham, MA, USA).

Oxidized regenerated cellulose and hyaluronate carboxymethylcellulose are both solid barrier films, and are difficult to apply during laparoscopic surgery. On the other hand, icodextrin is a fluid and PEG is a spray, making them easy to apply during laparoscopy. Formulation seems to impact the efficacy and adverse events profiles of barriers. It is generally believed that the solid and viscous gel barriers better prevent adhesion formation at sites of peritoneal injury and adhesiolysis, while liquid barriers better protect injured surfaces distant from surgical dissection areas (caused by retractors or desiccation, for example). However, there is no clear evidence for this hypothesis, even from animal experiments.

Despite the numerous clinical trials which have assessed the performance of these four barriers, their use remains somewhat controversial. For one of the most extensively studied barriers— hyaluronate carboxymethylcellulose—a trend toward increased abscess formation has been reported.(4;6) However, the increase was not significant in the final analyses of these studies, and was related only to a subgroup of patients where the barrier was wrapped around a fresh bowel anastomosis. The finding was also not reproduced in more recent studies where the barrier was not applied over a bowel anastomosis.(68-70) Nonetheless, the possibility continues to raise concern.

Regarding reoperations, a potential increase in abscess formation might actually be outweighed by the risks of adhesiolysis and SBO due to adhesion reformation. Unfortunately, most trials do not separately report barriers' efficacy for the subgroup of patients with pre-existing adhesions. In a recent systematic review, the controversy was addressed using a new method known as the error-matrix approach.(71) This method has been designed specifically for situations in which the benefits and harms of an intervention become difficult to weigh.(13) As the number of studies increases, published clinical evidence continues to expand but also becomes increasingly difficult to overview. Like with adhesion barriers, multiple trials with different outcome measures for efficacy and safety are often published for a single intervention. In a classic meta-analysis, the balanced results of a comparison need to be extracted from a large number of forest plots, each considering one specific outcome measure and including only a selection of the studies included. For example, in the review

conducted by Kumar and colleagues, ten different comparisons were made for five trials evaluating hyaluronate carboxymethylcellulose in general surgery alone.(72)

The error-matrix approach aides the process of reviewing the entirety of available evidence by assessing three dimensions: systematic error, random error, and design error. Systematic error is the risk of bias, and can be assessed using the Cochrane Collaboration's tool for bias risk assessment.(14) Random error is the risk of drawing a false conclusion based on sparse data, and is presented as the standard error (SE). Finally, among the many variables that should be considered in the design of a study, the relevance of different outcome measures are of central importance. Therefore, design error (external validity) is assessed by prospectively ranking the outcomes for their relevance to the patient. These three dimensions of error can be presented in a three-dimensional plot so that the relevance and strength of evidence for different benefits and harms of an intervention can be judged at a single glance.

Using the error-matrix approach, we found modest benefits for the use of oxidized regenerated cellulose and hyaluronate carboxymethylcellulose cellulose. Oxidized regenerated cellulose reduces adhesion formation following fertility surgery, but the impact on subsequent pregnancies has not been studied (Figure 3). Hyaluronate carboxymethylcellulose reduces operative time during two-stage liver surgery, and has a modest effect on the incidence of adhesive small bowel obstruction in colorectal surgery (Figure 4). Icodextrin (fluid) and PEG (spray) are easy to apply during laparoscopy, but their performance on clinically important outcomes is equivocal.(7;9)

THE AGENDA FOR THE FUTURE

Patient information

Patients undergoing abdominal surgery should be informed about the risk of adhesion-related complications. Surprisingly, patients are seldom informed about these risks despite the high incidence of adhesion-related complications. (73;74) In contrast, bile duct injury is mentioned in 82% of informed consents for laparoscopic cholecystectomy, whilst its incidence is far below one percent.(49;50) Epidemiologic data demonstrates that the complication rate of adhesiolysis during repeat surgery is well above the threshold at which no information is deemed negligence.

Clinical guidelines for adhesion prevention

The epidemiologic data on the burden of adhesiolysis and related complications has major implications for future adhesion prevention policies. To date, physicians and legislative bodies have focused on prevention of SBO as the main indicator of clinical success in adhesion prevention; however, morbidity and costs of adhesiolysis might exceed those of SBO. Reducing morbidity from adhesiolysis-related complications also appears to be a more feasible outcome of adhesion prevention for guidelines and clinical studies. Unfortunately, few comparative trials have investigated the impact of adhesion barriers on adhesiolysis-related outcomes.(25)

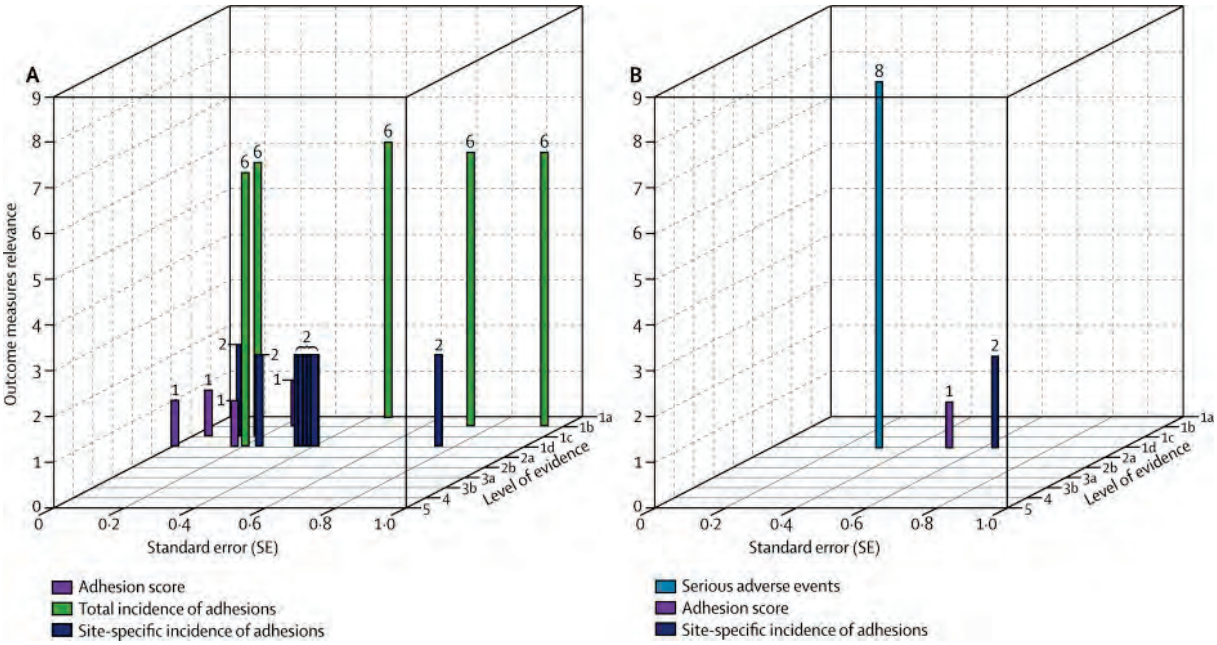


Figure 3. Manhattan plots summarizing benefits and harm of oxidized regenerated cellulose versus no adhesion barrier

Quick guide:
Systematic error (bias), plotted on the Y-axis, is measured by the level of evidence in which: 1A represents the meta-analysis of low-bias risk RCTs; 1B is a low-risk bias RCT; 1C is a meta-analysis of all RCTs, and 1D is a high- bias risk bias RCT. The X-axis represents random error measured by standard error (SE). A low risk for random error is defined as SE<0.20, and moderate risk as SE <1.00. Studies with a high risk for random error (SE>1.00) fall outside the range of the plot and are considered irrelevant for decision-making. Design error is plotted on the Z-axis, representing the relevance of the clinical outcome.

Results most important for clinical decision-making are plotted as the highest bars in the upper-left part of the plot.
a. Outcomes with benefit of oxidized regenerated cellulose versus none or placebo.
b. Outcomes with no difference or harm of oxidized regenerated cellulose versus none or placebo.

To find the evidence for oxidized regenerated cellulose influencing the incidence of adhesions, go to the green bars in figure 3 and read (1) Level of evidence (the risk of systematic error) and (2) standard error (the risk of random error).

From these Manhattan figures, one can see at a glance that there is evidence that oxidized regenerated cellulose shows benefit on the incidence of adhesions and on adhesions score with low risk of systematic error and low risk of random error.

A more detailed explanation of the error- matrix approach and Manhattan figures can be found elsewhere:
Keus F, Wetterslev J, Gluud C, van Laarhoven CJ. Evidence at a glance: error matrix approach for overviewing available evidence. BMC Med Res Methodol 2010; 10:90.

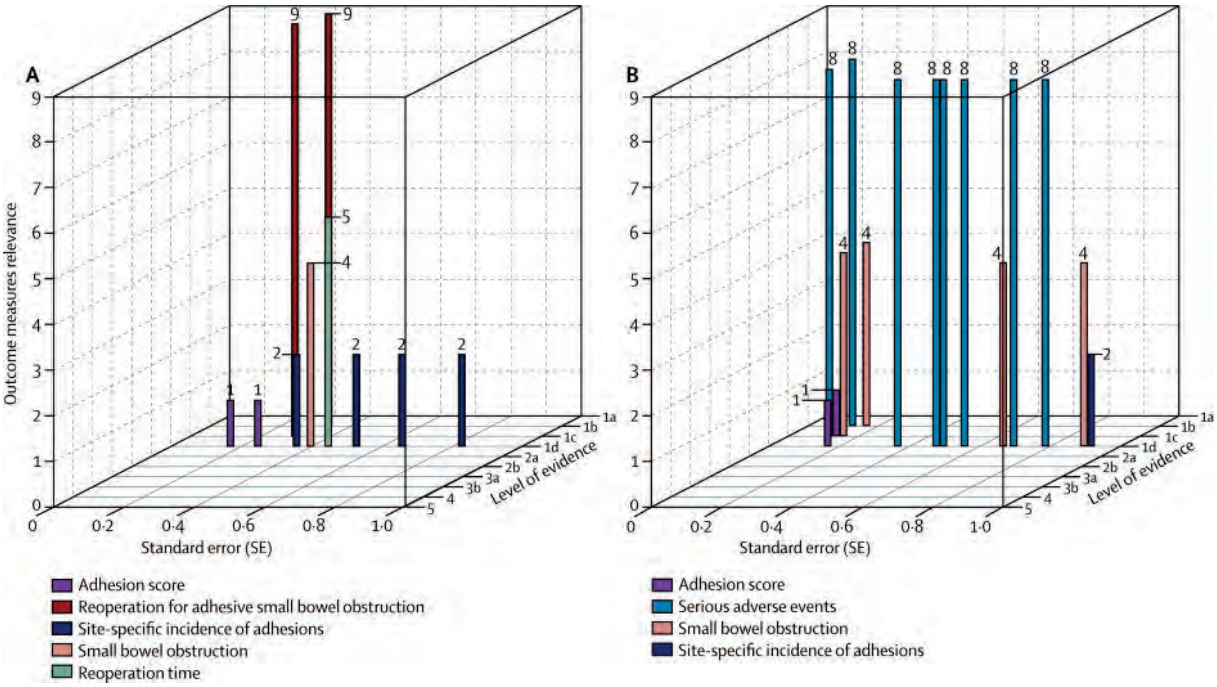


Figure 4 Manhattan plots summarizing benefits and harm comparing Hyaluronate carboxymethylcellulose versus no adhesion barrier

Manhattan-like three-dimensional matrix for hyaluronate carboxymethylcellulose, building upon the risks of systematic error, random error, and design error. The evidence with the lowest systematic, random, and design error is represented by the tallest bars, located on 'the upper left side'. A. Outcomes with benefit of hyaluronate carboxymethylcellulose versus none or placebo. B. Outcomes with harm of hyaluronate carboxymethylcellulose versus none or placebo.

From these Manhattan figures, one can see at a glance that there is evidence that hyaluronate carboxymethylcellulose trials show a beneficial effect on the incidence of reoperation for adhesive small bowel obstruction and operative time with low risk of systematic error and moderate risk of random error. There is no evidence of a beneficial effect on the incidence of serious adverse events in a large number of trials with varying risk of random error. Further, there is evidence that hyaluronate carboxymethylcellulose reduces the incidence of site-specific adhesions (blue bars) and adhesion scores (purple bars).

Reprinted from the Lancet with permission from Elsevier: ten Broek RP, Stommel MW, Strik C et al. Benefits and harms of adhesion barriers for abdominal surgery: a systematic review and meta-analysis. Lancet 2014;383;48-59.

Research on SBO prevention requires that a large number of patients be followed for many years. Most existing studies on prevention of SBO are therefore underpowered. Because of the relatively low incidence of SBO, many adhesion prevention agents are also unlikely to pay off in cost models when only counting the socioeconomic effects of SBO prevention.(49)

Prevention of difficulties during adhesiolysis, on the other hand, can be studied in two-stage operations.(15) Adhesiolysis-related complications are also more correlated to severity of adhesions. New cost-efficacy models that include the potential benefits of adhesion prevention in reoperations and fertility treatments are expected to indicate that prevention is also cost-effective in high risk surgeries, and will be applicable to a broader group of patients. Such high risk procedures include two-stage surgery, abdominal wall surgery, colorectal cancer surgery, and surgery with secondary prevention of adhesions (e.g. surgery for small bowel obstruction and fertility surgery).(56;75-77)

Challenges in adhesion prevention research

Despite the availability of a number of effective adhesion barriers, there is still a need for new and better agents for use in open and laparoscopic surgery. The development of new adhesion prevention agents faces several challenges in the coming decade, starting with the phase of pre-clinical studies. Animal models should be better standardized, and the studies should be performed with sample sizes that have sufficient power. Improving animal studies would avoid perpetuating the excess of duplicate studies with contradicting results, and would enhance translational value by using more meaningful outcomes, such as incidence of adhesions and secondary prevention of adhesions.

Research on the pathophysiology of adhesions has revealed a large number of adhesion formation mediators, including collagen I, fibronectin, matrix metalloproteinase-1 (MMP-1), tissue inhibitor of metalloproteinase-1 (TIMP-1), transforming growth factor (TGF)-β1, cyclooxygenase-2 (COX-2), interleukin (IL)-10, and the tissue plasminogen activator (tPA) and plasminogen activator inhibitor type-1 (PAI-1) ratio.(67;78) Although these studies have enhanced our understanding of adhesion formation, they have not yet resulted in clinically effective targeted therapies.(67) Clinical studies with rPA are still in their infancy, however, and some promising animal experiments are currently being performed with intraperitoneal therapy targeting the Neurokinin 1 receptor. (79;80),(15) Clinical trials are needed to demonstrate if such targeted therapies are effective in reducing postoperative adhesion formation. Moreover, widespread implementation will require extensive research on safety and potential harmful effects under different circumstances such as bowel anastomosis, peritonitis, and blood contamination.

At present, there are few pivotal studies which have used outcomes of clinical importance to the patient such as pregnancy rate, adhesive small bowel obstruction, and chronic pain. The difficulty with measuring these outcomes in clinical trials is the large time span in which these outcomes develop.(50;81) To study such endpoints, large numbers of patients need to be randomized and followed for many years. Because of these difficulties, scoring of adhesions during a second look operation has been popularized as a proxy for the risk of adhesion-related complications. With the growing epidemiologic knowledge that adhesiolysis-related complications are the most important complication from adhesions, we believe this proxy should also be an acceptable efficacy outcome for regulatory bodies. Again, however, incidence of adhesions should be the preferred outcome measure rather than subjective adhesion scores.

Non invasive diagnosis of adhesions

Diagnosis of adhesion-related complications is challenging, given that second look surgery and emergent reoperation are the only current means of establishing the incidence of adhesions and adhesive small bowel obstruction. The number of planned second procedures has declined both in female patients following fertility surgery or myomectomy, and in patients who are scheduled for two-stage benign colorectal surgery with planned enterostomy take down. (82-84) Obviously, performing a diagnostic second operation solely for the purpose of research is ethically unacceptable since it exposes the patient to risk for inadvertent organ injury. Furthermore, adhesions lysed during the second procedure might re-form.

Cine-MRI might eventually replace the second look operation as a non-invasive alternative for diagnosis of adhesions, and as an outcome for clinical studies on adhesion prevention. 'Visceral slide' of bowel loops adjacent to the abdominal wall on ultrasound or cine-MRI has a high prognostic value for adhesions. Ultrasound does not enable ‘visualizing’ adhesions deeper in the abdominal cavity. By contrast, the full abdominal cavity can be imaged with cine-MRI. However, results need to be validated with intra- operative findings before cine-MRI can be accepted as a valid non-invasive tool with which to map adhesions.

Summary

The biggest challenges in adhesion research for the coming decade are:

- Development of evidence-based clinical guidelines for adhesion prevention
- Development of efficacious adhesion-preventing agents suitable for both open and laparoscopic use
- Standardization of both preclinical and clinical adhesion studies
- Development and validation of non-invasive diagnostic tools for adhesions, such as cine-MRI

CONCLUSIONS

Despite mounting evidence that adhesions are the most common complication in abdominal surgery, little progress has been made over the past two decades both in preventing adhesions and in informing patients about their risks. There is increasing evidence that difficulties related to adhesiolysis in reoperations are the biggest adhesion-related complication. Now that the efficacy of adhesion barriers has been established for reducing the incidence of adhesion-formation, research should focus on implementation strategies and on selecting patient groups that will benefit most. Additional research also remains necessary to develop new, cost-effective barriers that are suitable for laparoscopic use. Finally, both animal and clinical studies on adhesion formation need a higher degree of standardization so that advances in adhesion prevention strategies can be implemented faster and with broader acceptance in clinical practice.

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SUMMARY

Abdominal surgery is frequently performed by a multitude of specialists, such as general, vascular, urological and gynaecological surgeons. From the SCAR study it is known that 55 000 patients undergo abdominal surgery in one year in Scotland, which number is more than one per cent of the entire population. In the Netherlands more than 24 000 operations of the lower gastro- intestinal tract are performed annually, procedures with high risk of adhesion formation.
Adhesions form in 60% to 90% of patients after abdominal surgery. Postoperative adhesions cause a life-long risk of different complications including small bowel obstruction, difficulties at re-operations, chronic abdominal pain, and secondary female infertility. These complications can be found after all types of abdominal surgery, performed by surgeons, gynaecologists or urologists. Till date most reports on the clinical and socioeconomic impact of adhesion related complications had their focus on adhesive small bowel obstruction. Adhesiolysis at repeat surgery received much less attention in literature. Underestimation of adhesiolysis related morbidity may account for the paucity of reports on this consequence of adhesions.
Since the 90's several adhesion barriers have been developed and marketed but prevention of adhesion formation is seldom applied. Many questions still exist among surgeons and gynaecologists on the efficacy and safety of adhesion barriers.
In the current thesis the awareness of adhesion related complications by clinicians is addressed, the impact of adhesions at repeat surgery is extensively studied and the current knowledge of adhesion prevention is systematically reviewed.

Part I: awareness of adhesion related complications.
CHAPTER 2 described the results of a systematic review and meta-analysis of 196 cohort studies on the incidence of various adhesion related complications. Almost 1 in 10 patients had an episode of small bowel obstruction after abdominal operation. In patients with a known cause, adhesions were the single most common cause of bowel obstruction. The incidence of adhesive small bowel obstruction was 2% (95% confidence interval 2% to 3%; I^2=93%); presence of adhesions was generally confirmed by emergent reoperation. Operative time was significantly prolonged in patients with previous surgery, and performing adhesiolysis caused a significant risk of iatrogenic bowel injury. The review provides detailed knowledge analysed in a systematic way of the disease burden of adhesions. Complications of postoperative adhesion formation are frequent, have a large harmful effect on patients' health, and increase workload in clinical practice.

In CHAPTER 3 we presented the results of a questionnaire testing the knowledge of Dutch surgeons of adhesion related complications and exploring their attitude towards adhesions and anti- adhesion agents. The questionnaire was returned by more than 500 surgeons and residents. Knowledge scores (mean test score percentage 37.6) were low illustrating the underestimation of the incidence and impact of adhesions. Two thirds of all respondents (67.7%) agreed that adhesions exert a clinically relevant and negative effect. A majority of surgeons (55.9%) used anti-adhesion agents in the past, but only a minority (13.4%) did so in the previous year. Less than 10% of surgeons routinely inform their patients on the risks of adhesions. In conclusion, the magnitude of the clinical burden of postoperative adhesions is

underestimated and informed consent is provided inadequately by Dutch surgeons. Application of an adhesion barrier is not routine.

CHAPTER 4 explored how accurate adhesion related complications during reoperations are described in operative reports as a proxy for the awareness level of the clinical burden of adhesions. For this purpose we compared real-time observations from a research database with the operative reports of 755 procedures. Sensitivity and specificity for the incidence of adhesions was 85.1 and 72.4 per cent respectively. Six of 43 inadvertent enterotomies, and 17 of 48 other organ injuries, had not been reported. Documentation of inadvertent enterotomies was missing more often in delayed reports (2 of 3 versus 1 of 10 in reports dictated with no delay; P=0.022). Performing adhesiolysis and subsequent organ injury are often neglected in operative reports.

Part II: difficulties of adhesions during reoperations

CHAPTER 5 and 6 described the findings of the LAPAD study. The LAPAD study is a prospective cohort study designed to assess data on adhesiolysis and inadvertent organ injury that were gathered by direct observation during operation. Further, detailed medical history and postoperative course data were registered. CHAPTER 5 described the results for the whole cohort of operations through an abdominal incision, in CHAPTER 6 we focussed on patients undergoing abdominal wall reconstruction.

A total of 755 surgeries in 715 patients were included. Adhesiolysis was required in 475 (62.9%) operations. Median adhesiolysis time was 20 minutes (range: 1–177). Fifty patients (10.5%) who underwent adhesiolysis inadvertently incurred a bowel defect, compared to zero without adhesiolysis ($P < 0.001$). In univariate and multivariate analyses, adhesiolysis was associated with an increase of sepsis incidence [odds ratio (OR): 5.12; 95% confidence interval (CI): 1.06–24.71], intra-abdominal complications (OR: 3.46; 95% CI: 1.49–8.05) and wound infection (OR: 2.45; 95% CI: 1.01–5.94), longer hospital stay (2.06 ± 1.06 days), and higher hospital costs [$18,579 (15,204–21,954) *vs* $14,063 (12,471–15,655)]. Mortality after adhesiolysis complicated by a bowel defect was 4 out of 50 (8%), compared with 7 out of 425 (1.6%) after uncomplicated adhesiolysis (OR: 5.19; 95% CI: 1.47–18.41).

Adhesiolysis was required in 124 (93.2%) of 133 abdominal wall reconstruction, with a mean adhesiolysis time of 35.7 ± 29.8 minutes. Thirty-three enterotomies were made in 17 patients (12.8%). Two patients had a delayed diagnosed bowel perforation. Adhesiolysis time, hernia size greater than 10 cm, and fistula were significant predictive factors in univariate analysis. In multivariate analysis, only adhesiolysis time was a significant and independent predictive factor for enterotomy ($P = 0.004$).

Adhesiolysis and inadvertent bowel injury have a harmful effect on the convalescence after abdominal surgery. Adhesiolysis is complicated by an inadvertent bowel injury in 10 percent of operations. Bowel injuries are associated with higher postoperative mortality, longer hospital stay and increased health care utilization.

In CHAPTER 7 we described the development of a prediction model, scoring the risk for inadvertent enterotomy based on preoperative factors. The number of previous laparotomies, anatomical site of the operation, presence of bowel fistula and laparotomy via a pre-existing

median scar were independent predictors of bowel injury. A scoring system and nomogram were constructed incorporating these four risk factors. The area under the receiver operating characteristic curve was 0.85. The predicted risk in patients positive on all four risk factors was 50%. The nomogram accurately predicts the risk for bowel injury and can readily be used to identify high- risk patients.

Part III: Adhesion prevention

In CHAPTER 8 evidence for the impact of different surgical techniques on adhesion formation was reviewed in a systematic way from randomized trials. Surgical technique has been poorly investigated in relation to adhesion formation. A total of 27 papers were included, most of them of low quality. None of the techniques that were compared significantly reduced the incidence of adhesive small bowel obstruction. In a small low quality trial, the pregnancy rate increased after subserous fixation of suture knots. The incidence of adhesions was lower after laparoscopic then after open surgery [relative risk (RR) 0.14; 95% confidence interval (CI): 0.03-0.61] and when the peritoneum was not closed (RR 0.36; 95% CI 0.21-0.63). None of the different techniques reduced the incidence of clinical outcomes critical for decision making, such as small bowel obstruction and infertility. The meta-analysis provides some evidence to the surgical principle that less invasive techniques, less foreign bodies and less ischemia reduce the incidence, extent and severity of adhesions.

In CHAPTER 9 we compared the peritoneal tissue damage caused by two popular hemostatic devices, monopolar electrocautery and ultrasonic dissection. 18 Wistar rats underwent a median laparotomy and had a peritoneal microdialysis catheter implanted in the left lateral sidewall. The animals were randomly assigned to receive two standard peritoneal incisions parallel to the catheter by either ultrasonic dissection or electrocautery. After the operation, samples of microdialysis dialysate were taken every two hours until 72 hours postoperatively. The mean lactate–pyruvate ratio (LPR), lactate–glucose ratio (LGR), and glycerol concentration were significantly higher in the electrocautery group than in the ultrasonic dissection group until 34, 48, and 48 hours after surgery respectively. The mean areas under the curve (AUC) of LPR, LGR, and glycerol concentration also were higher in the electrocautery group than in the ultrasonic dissection group, indicating more ischemic peritoneal damage from electrocautery. Using ultrasonic dissection might aid in reducing adhesion formation.

In CHAPTER 10 we evaluated the evidence of benefits and harm of four commercially available adhesion barriers. In this systematic review and meta-analysis, we searched PubMed, CENTRAL, and Embase for randomised clinical trials assessing use of oxidised regenerated cellulose, hyaluronate carboxy methylcellulose, icodextrin, or polyethylene glycol in abdominal surgery. We compared use of a barrier with no barrier for nine predefined outcomes, graded for clinical relevance. The primary outcome was reoperation for adhesive small bowel obstruction. We assessed systematic error, random error, and design error with the error matrix approach. The risks of systematic and random errors were low. No trials reported data for the effect of oxidised regenerated cellulose or polyethylene glycol on reoperations for adhesive small bowel obstruction. Oxidised regenerated cellulose reduced the

incidence of adhesions (relative risk [RR] 0.51, 95% CI 0.31–0.86). Some evidence suggests that hyaluronate carboxymethylcellulose reduces the incidence of reoperations for adhesive small bowel obstruction (RR 0.49, 95% CI 0.28–0.88). For icodextrin, reoperation for adhesive small bowel obstruction did not differ significantly between groups (RR 0.33, 95% CI 0.03–3.11). No barriers were associated with an increase in serious adverse events. Oxidised regenerated cellulose and hyaluronate carboxymethylcellulose can safely reduce clinically relevant consequences of adhesions.

In CHAPTER 11 the results of a small pilot study on the efficacy of polyethylene glycol (PEG) adhesion barrier in gynaecological laparoscopies are described. The trial was aborted after including only 16 patients for organizational difficulties. Still we found some evidence for the efficacy of PEG adhesion barrier. At second look operation, the incidence of *de novo* adhesion was lower in the PEG group (0/9 vs. 4/6; P=0.01). Reduction in adhesion score was significantly greater in patients receiving PEG barrier (-2.6 vs. -0.06, P = 0.03). More importantly, the paper illustrates the difficulties in organizing a randomized trials of adhesion barriers. The number of planned second look procedures is rapidly declining in fertility surgery, making it difficult to include sufficient numbers of patients. Also the additional costs and ethical considerations for patients participating in such trials and undergoing a second operations for in part research purpose should be taken into account when designing such trials.

CHAPTER 12 is the discussion and future perspectives of this thesis. It highlights the developments in the field of adhesion research for the past decade. Although adhesion barriers have now been around for more than a decade, adhesion prevention is seldom applied. The main reasons for this seem a continuing lack of awareness regarding the burden of adhesion related complications, questions on the indications and cost-efficacy of adhesions barriers, and safety concerns. New epidemiologic data warrant a paradigm shift in our understanding of the socioeconomic burden of adhesion related complications and the indications for adhesion prevention strategies. Increasing evidence from cohort studies and systematic reviews show that difficulties during reoperations rather than small bowel obstructions account for the majority of adhesion related morbidity. New cost-efficacy models that include the potential benefits of adhesion prevention in reoperations and fertility treatments are expected to indicate that prevention is also cost-effective in high risk surgeries for adhesion formation and should be applied to a broader group of patients. More effort should be put into improvement of research on adhesion prevention from molecule to man to population. Animal models need to be better standardized and powered to generate more meaningful and robust results. There is a need for non- invasive techniques to assess adhesion formation in clinical trials. Cine-MRI holds promise, but needs further development.

Summary in Dutch (Nederlandse samenvatting)

Buikoperaties worden vaak uitgevoerd door diverse specialisten, onder wie algemeen chirurgen, vaatchirurgen, urologen en gynaecologen. Het is precieze aantal buikoperaties is moeilijk in te schatten. Tijdens de SCAR studie onderging ruim één procent (55.000) van de totale bevolking van Schotland binnen een jaar tijd voor het eerst een buikoperatie. In Nederland worden ieder jaar meer dan 24.000 operaties van de onderste tractus digestivus verricht. Deze procedures zijn bekend vanwege hun hoge risico op adhesie vorming. Adhesies vormen zich in 60% tot 90% van de patiënten die een buikoperatie hebben ondergaan. Daarmee zou adhesie vorming als een normaal onderdeel van het genezingsproces van een buikoperatie kunnen worden gezien. Echter, adhesies hebben vaak secundaire gevolgen. Deze gevolgen zijn divers en kunnen soms pas vele jaren na de oorspronkelijke operatie optreden. De belangrijkste daarvan zijn een obstructie van de darm; complicaties bij heroperaties; chronische pijn; en onvruchtbaarheid bij vrouwen. Deze gevolgen van adhesies komen voor na alle soorten buikoperaties. Tot op heden is het onderzoek naar verklevingen vooral gericht op de morbiditeit en maatschappelijke gevolgen van een acute darmobstructie. De problemen bij heroperaties door het moeten verrichten van een adhesiolyse, zijn veel minder belicht in de medische literatuur. Het lijkt erop dat de gevolgen van adhesiolyse vaak worden onderschat.
Sinds de jaren ’90 zijn er diverse middelen ontwikkeld om adhesie vorming te voorkomen of te remmen, ook wel adhesie ‘barriers’ genoemd. Deze worden echter maar zelden toegepast. Dit komt waarschijnlijk omdat chirurgen en gynaecologen veel vragen hebben over de veiligheid en effectiviteit van deze middelen.
In dit proefschrift beschrijven wij: het bewustzijn (awareness) van zorgverleners ten aanzien van complicaties gerelateerd aan adhesies, de gevolgen van adhesies bij heroperaties, en preventie van adhesies.

Deel 1: ‘Awareness’ van complicaties gerelateerd aan adhesies
In HOOFDSTUK 2 beschreven wij in een systematische review en meta-analyse de resultaten van 196 studies over de prevalentie van één of meer complicaties gerelateerd aan adhesies. Negen procent (95% betrouwbaarheidsinterval [BI]: 7%- 10%) van de patiënten die een buikoperatie hebben ondergaan ontwikkelen hierna een darmobstructie. Vaak kan de oorzaak niet betrouwbaar worden vastgesteld. Sommige oorzaken, zoals adhesies, zijn alleen zeker als er wordt geopereerd. De prevalentie van een darmobstructie die met zekerheid is veroorzaakt door adhesies is daarom lager, 2% (95% BI: 2%- 3%). De darmobstructies die met zekerheid door adhesies zijn veroorzaakt betreffen wel 56% (95% BI: 49%- 64%) van alle gevallen van ileus waarin de oorzaak bekend is. Hiermee zijn adhesies met afstand de meest voorkomende oorzaak voor acute darmobstructie. Bij heroperaties verlengt een adhesiolyse de operatietijd met gemiddeld 15 min (95% BI: 9.3- 21.1 min). Bij 6% (95% BI: 4% - 8%) veroorzaakt het verrichten van een adhesiolyse zelfs onbedoelde darmschade. Vrouwelijke patiënten met inflammatoire darmziekte die zijn geopereerd worden significant minder vaak zwanger dan patiënten die alleen medicamenteus zijn behandeld (50% [95% BI: 37%-63%] vs. 82%[95% BI: 70%- 94%]). In deze review hebben wij systematisch en gedetailleerd de gevolgen van adhesievorming beschreven. Complicaties van verklevingen komen vaak voor en hebben een negatief effect op de gezondheid van patiënten en veroorzaken een toename van gezondheidszorgkosten.

HOOFDSTUK 3 beschrijft de resultaten van een enquête onder Nederlandse chirurgen met een kennistoets over adhesies en vragen over de attitude van chirurgen ten aanzien van adhesies en adhesiepreventie. Ruim 500 chirurgen en assistenten in opleiding hadden de enquête volledig ingevuld. Op de kennistoets over de gevolgen van adhesies was het gemiddelde percentage goede antwoorden slechts 37.6%. Bovendien betroffen de meeste foutieve antwoorden een onderschatting van de ernst van het probleem. Wel was 67.7% van de chirurgen het erover eens dat adhesies belangrijke negatieve gevolgen hebben voor patiënten die een buikoperatie ondergaan. Anti- adhesie middelen zijn weinig toegepast. Hoewel 55.9% van de chirurgen aangeeft ooit een anti- adhesie middel te hebben gebruikt, had slechts 13.4% dit in het afgelopen jaar gedaan. Bovendien bleken er veel vragen te bestaan over de indicaties voor het gebruik van anti- adhesie middelen. Nog geen 10% van de chirurgen bespreekt routinematig de risico's van adhesies met zijn patiënten. Concluderend onderschatten Nederlandse chirurgen de gevolgen van adhesies en bespreken zij ook zelden met patiënten de risico's van adhesies. Adhesie barriers worden niet routinematig gebruikt.

In HOODSTUK 4 bestudeerden wij hoe betrouwbaar het voorkomen van adhesies en het verrichten van een adhesiolyse tijdens een operatie worden beschreven in het operatieverslag, als afgeleide maat voor de awareness van adhesies. Hiertoe vergeleken wij de officiële operatieverslagen van 755 operaties met de bevindingen die tijdens deze operaties werden geregistreerd door de onderzoekers van de LAPAD studie in een real- time database. De sensitiviteit en specificiteit van adhesies in operatieverslagen bedroegen respectievelijk 85.1% en 72.4%. Bovendien werden 6 van de 43 enterotomiën en 17 van de 48 andere orgaanletsels niet vermeld. Bij operatie verslagen die te laat waren gedicteerd was het percentage gemiste enterotomiën hoger (2/3 tegenover 1/10 bij tijdig gedicteerde verslagen; P=0.022) . Het verrichten van adhesiolyse en daarop volgende orgaanschade wordt te vaak niet vermeld in operatieverslagen.

Deel 2: Problemen die adhesies veroorzaken bij heroperaties

In HOOFDSTUK 5 en 6 beschrijven wij de resultaten van de LAPAD studie. In deze studie brachten wij voor het eerst de problemen van heroperaties op systematische en prospectieve wijze in kaart. Twee jaar lang werden alle patiënten gevolgd die waren opgenomen op de afdeling heelkunde van het RadboudUMC voor het ondergaan van een electieve buikoperatie. Relevante medische gegevens werden verzameld voor, tijdens en na de operatie. Tijdens de operaties werd door een kleine toegewijde groep onderzoekers, aanwezig op de operatiekamers, gegevens over de incidentie en ernst van adhesies geregistreerd in een real-time database. Ook werd het al of niet verrichten van adhesiolyse geregistreerd en de tijdsduur van deze adhesiolyse gemeten. Op basis van deze gegevens kon een zeer nauwkeurig beeld van de impact van adhesies op het verloop van de operatie en postoperatieve complicaties worden verkregen. HOOFDSTUK 5 beschrijft de resultaten van de gehele groep. HOOFDSTUK 6 richt zich op de subgroep van patiënten die een buikwandreconstructie onderging.

In totaal werden 755 operaties, verricht bij 715 patiënten, geïncludeerd. Adhesiolyse werd verricht in 475 (62.9%) van alle operaties. De mediane adhesiolyse tijd bedroeg 20 minuten

(variërend van 1 tot 177 minuten). Vijftig operaties (10.5%) werden gecompliceerd door onbedoelde darmschade. Darmschade trad alleen op bij patiënten die adhesiolyse hadden ondergaan (P<0.001). Zowel in de univariaat als multivariaat analyse was adhesiolyse (met of zonder darmschade) geassocieerd met een toegenomen incidentie van sepsis (Odds Ratio [OR]: 5.12; 95% BI: 1.06- 24.7), intra- abdominale complicaties (OR 3.46; 95% BI: 1.49- 8.05) en wondinfectie (OR 2.45; 95% CI: 1.01- 5.94). Boven was de gemiddelde ziekenhuisduur 2 dagen langer en waren de ziekenhuiskosten hoger [$18,579 (15,204–21,954) *vs* $14,063 (12,471–15,655)]. Na onbedoelde darmschade was het risico op overlijden tijdens de opname significant hoger (8% vs. 1.6%; OR 5.19; 95% BI: 1.47-18.41).
Bij 124 van de 133(93.2%) buikwandreconstructies werd adhesiolyse verricht. De gemiddelde adhesiolyse tijd bedroeg 35.7 ± 29.8 minuten. In totaal werden 33 enterotomiën gemaakt in 17 patiënten (12.8%). Verder hadden 2 patiënten darmschade die pas postoperatief werd gediagnosticeerd. De tijdsduur van adhesiolyse, een buikwandbreuk groter dan 10 cm, en fistels waren risicofactoren voor darmschade. In de multivariaat analyse was alleen de tijdsduur van adhesiolyse een onafhankelijke voorspeller voor darmschade (P=0.004).
Het verrichten van adhesiolyse en daaropvolgend orgaanschade heeft een groot negatief effect op het herstel van patiënten die een buikoperatie ondergaan. Adhesiolyse gaat gepaard met onbedoelde darmschade in ongeveer 1 op 10 operaties. Darmschade gaat gepaard met hogere sterfte na operatie, een langere ligduur en hogere ziektekosten.

HOOFDSTUK 7 beschrijft de ontwikkeling van een scoremodel, gebaseerd op de LAPAD studie, om het risico op een enterotomie pre- operatief in te schatten. Onafhankelijke voorspellende variabelen voor het risico op een enterotomie zijn: het aantal buikoperaties in de voorgeschiedenis, de anatomische locatie van de geplande operatie, aanwezigheid van entero- cutane fistels en een buikoperatie door een bestaand litteken van een mediane laparotomie. Op basis van deze variabelen werd een model gemaakt om het risico op enterotomie te voorspellen. Het model geeft een nauwkeurige voorspelling van de patiënten met een hoog risico op darmschade. De ‘area under the receiver operating characteristic curve’ was 0.85. Het voorspelde risico op darmschade in de hoogste risicogroep was 50%. Van dit model is ook een nomogram gemaakt wat makkelijk gebruikt kan worden in de voorlichting van patiënten en voor het identificeren van patiënten met een hoog risico op darmschade.

Deel 3: Preventie van adhesies
In HOOFDSTUK 8 beschrijven wij een meta- analyse van alle gerandomiseerde onderzoeken die verschillende chirurgische technieken vergelijken op uitkomsten gerelateerd aan adhesies. Er werden 27 studies geïncludeerd, de kwaliteit van de meeste van deze studies was laag en er konden vaak geen duidelijke conclusies worden getrokken. Het risico op darmobstructie is in geen van de studies onderzocht. In een kleine studie binnen de fertiliteitschirurgie was de kans op zwangerschap groter wanneer de hechtingen subsereus werden gefixeerd. De incidentie van verklevingen lijkt lager na een laparoscopische ingreep vergeleken met een open buik operatie [Relatief risico (RR) 0.14; 95% betrouwbaarheidsinterval (BI): 0.03-0.61], en wanneer het peritoneum niet wordt gesloten aan het eind van een ingreep (RR 0.36; 95% BI 0.21-0.63).

Geen van de vergeleken technieken toonde duidelijk bewijs op klinisch harde eindpunten zoals ileus of zwangerschappen. Wel wordt enig bewijs gevonden dat minimaal invasieve technieken, beperking van vreemd lichaam, en het verminderen van ischemische schade, de incidentie en uitgebreidheid van verklevingen beperkt.

HOOFDSTUK 9 beschrijft een dierstudie waarin twee veel gebruikte moderne instrumenten om te prepareren en bloedingen te verzorgen in de buikchirurgie worden vergeleken op de schade die ze aanrichten aan het peritoneum. De eerste is een diathermisch mes, waarbij energie wordt afgegeven in de vorm van hoogfrequente stroom. Het tweede instrument is een ‘ultrasonore dissectie haak’, waarbij energie in de vorm van een ultrageluidstrilling wordt afgegeven. 18 Wistar ratten werden gerandomiseerd voor het ondergaan van een gestandaardiseerde procedure met of diathermie of ultrasonore dissectie. De schade aan het peritoneum werd gemeten met microdialyse waarbij iedere 2 uur, tot 72 uur na de ingreep, markers van peritoneale schade werden bepaald in het dialysaat. Deze markers betroffen de lactaat-pyruvaat ratio (LPR), lactaat-glucose ratio (LGR) en glycerol concentratie. De LPR, LGR en glycerol concentratie waren significant hoger in de diathermie groep tot respectievelijk 34, 48 en 48 uur na de ingreep. De ‘area under curve’ van de LPR, LGR en glycerol concentratie was ook significant hoger in de diathermie groep, wat erop duidt dat de peritoneale schade ten gevolge van diathermie groter is dan die van ultrasonore dissectie. Het gebruik van een ultrasonore dissectie kan dus nuttig zijn om adhesie vorming te beperken.

In HOOFDSTUK 10 deden we een systematische review en meta-analyse over de voor- en nadelen van vier commercieel beschikbare adhesie barriers. Voor deze analyse hebben wij gebruik gemaakt van een nieuwe meta-analyse techniek, namelijk de error-matrix approach. Deze techniek heeft als voordeel dat er snel een overzicht kan worden gegeven van alle voor- en nadelen van een interventie, in tegenstelling tot klassieke meta-analyse technieken waarbij per analyse steeds slechts één uitkomst wordt geëvalueerd. In totaal 9 vooraf gedefinieerde uitkomsten werden bestudeerd. Heroperatie voor een darmobstructie veroorzaakt door adhesies was de primaire uitkomst. Na een uitgebreide search in Pubmed, EMBASE en CENTRAL werden 28 gerandomiseerde onderzoeken met 5.191 patiënten geïncludeerd. Het risico op systematische fouten was laag. 'Hyaluronate carboxymethylcellulose' verminderde het risico op heroperaties voor darmobstructie (RR 0.4 9, 95% BI: 0.28- 0.88). 'Oxidised regenerated cellulose' verminderde de incidentie van adhesies in gynaecologische operaties (RR 0.51, 95% BI: 0.31- 0.86). ' Geen van de vier barriers was geassocieerd met een toename in chirurgische complicaties.
Gebruik van deze barriers is veilig en leidt niet tot een verhoogde incidentie van complicaties. ’ Oxidised regenerated cellulose’ en 'hyaluronate carboxymethylcellulose' hebben beide bewezen het risico op klinisch relevante gevolgen van adhesies te verminderen.

HOOFDSTUK 11 beschrijft een kleine studie naar de effectiviteit van het anti- adhesie middel polyethylene glycol. De studie moest vervroegd worden afgebroken wegens organisatorische redenen, nadat 16 patiënten waren geïncludeerd. In deze kleine groep werden toch aanwijzingen gevonden voor effectiviteit van dit middel. De incidentie van nieuwe adhesies was lager tijdens de tweede kijkoperatie (0/9 vs. 4/6; P=0.01), en de afname in

adhesie score groter (-2.6 vs. -0.06; P=0.03). Belangrijker is echter dat deze studie de moeilijkheden onderstreept bij het uitvoeren van studies met anti- adhesie middelen in de huidige tijd. Het aantal geplande kijkoperaties nam de afgelopen jaren sterk af, ook in de fertiliteitschirurgie, waardoor het includeren van voldoende patiënten waarbij adhesie vorming tijdens een tweede operatie kan worden beoordeeld steeds lastiger wordt. Verder vereisen verzekeringen voor proefpersonen een polis voor beide ingrepen. Voor nieuwe studies moet gekeken worden naar nieuwe (niet- invasieve) uitkomsten om adhesie vorming te beoordelen.

HOOFDSTUK 12 vormt de discussie van dit proefschrift. Er wordt een overzicht gegeven van de 'highlights' op het gebied van adhesieonderzoek in het afgelopen decennium, zoals beschreven in dit proefschrift en daarbuiten. Hoewel adhesie barriers in het afgelopen decennium commercieel beschikbaar waren, zijn deze zelden gebruikt. Belangrijkste redenen lijken het onderschatten van de gevolgen van adhesies, vragen rondom veiligheid van adhesie barriers, en vragen omtrent kosteneffectiviteit. De groeiende kennis over de impact van adhesiolyse tijdens heroperaties, noopt tot een verandering in de benadering van adhesies en preventie daarvan. Niet ileus, maar adhesiolyse veroorzaakt de meeste morbiditeit en maatschappelijke kosten gerelateerd aan adhesies. Nieuwe onderzoeken en kostenmodellen zouden daarom ook deze uitkomsten moeten meenemen. Verder is het ook noodzaak om het onderzoek naar adhesies preventie te verbeteren, vanaf het laboratorium naar de patiënt en tot op populatie niveau. Dierstudies moeten beter gestandaardiseerd worden en uitgevoerd met voldoende proefdieren, zodat zij betere en meer betrouwbare resultaten kunnen laten zien. Voor klinisch onderzoek is er een grote behoefte aan niet- invasieve diagnostiek van adhesies. Cine- MRI is veelbelovend, maar moet nog verder worden ontwikkeld voor het aantonen van adhesies.

Acknowledgements (Dankwoord)

Velen hebben direct of indirect bijgedragen aan het tot stand komen van dit proefschrift. Mijn dank gaat uit naar allen, maar een aantal wil ik hier in het bijzonder vermelden.

Prof. H. van Goor, Beste Harry,
Ik weet nog goed dat ik als eerstejaars geneeskunde student aan je vroeg of ik onderzoek mocht komen doen bij de chirurgie. Met dank aan jouw inzicht en enthousiasme voor onderzoek is dat traject steeds verder, in positieve zin, uit de hand gelopen. Ik ben je dankbaar voor het vertrouwen en de kansen die je mij hebt gegeven. Ik vind het een eer om één van de eerste promovendi te zijn met professor Harry als promotor.

Prof. C.J.H.M. van Laarhoven, Beste Kees,
Mede dankzij jouw visie en inzet hebben we unieke onderzoeksprojecten kunnen opzetten, zoals de LAPAD studie, binnen de afdeling chirurgie in het RadboudUMC. Ik ben je zeer dankbaar voor het vertrouwen. Er is hard gewerkt om deze projecten tot een goed einde te brengen, maar zoals ze in Tilburg zeggen ´agge moar leut het´.

Mijn dank gaat uit naar de leescommissie **Prof. G.J. van der Wilt, Prof. Prof. W.A. Bemelman, en Prof. L.F.A.G. Massuger.** Bedankt voor de tijd en moeite die u heeft gestoken in het beoordelen en vervolmaken van mijn proefschrift.

Dr. N.D. Bouvy, Beste Nicole,
Het Maastrichtse fundament van de Dutch Adhesion Group. Ik heb veel waardering voor je enthousiasme, inzet en persoonlijkheid. Gedreven, innoverend maar ook zuidelijke gezelligheid. Ik vind het een eer dat je vandaag in mijn corona aanwezig bent.

Dr. E.A. Bakkum, Beste Erica,
Onderzoek doe je samen en adhesies bestrijden ook. Ik vind het een enorme verrijking dat we in Dutch Adhesion Group als chirurgen en gynaecologen samen optrekken. Je inbreng inspireert steeds weer om over de muren van onze vakgebieden te kijken.

Drs. M.H.F. Schreinemacher, Beste Marc,
Op het snijvlak van de chirurgie en ZZ-top heb je de sharp-dressed-man die volgens SCHERP wordt opgeleid. Altijd optimistisch, wetenschappelijk kritisch, en bereid om een extra mile te gaan. Het is een genoegen om met je samen te werken.

Drs. C. Strik, Beste Chema,
Onze nieuwe ster aan het Dutch Adhesion Group firmament. Maar ook voordat je begon te werken aan je eigen proefschrift al van onschatbare waarde. Na mijzelf de meeste patiënten voor de LAPAD geïncludeerd, manusje van alles en niet te vergeten... nooit te beroerd om in de periode toen ik in Ede en Doetinchem werkte, op soms vreemde tijden, naar het Radboud te fietsen als ik weer eens problemen had met het telewerken. Je doorzettingsvermogen heeft je al naar de eindstreep van de Marathon van Rotterdam gebracht, en ik ben ervan overtuigd dat het je ook tot de eindstreep van een promotie brengt.

Drs. M.W.J. Stommel, Beste Martijn,
Tijdens mijn coschappen vertelde ik ooit aan een Belgische orthopeed dat ik onderzoek deed naar adhesies. Daarop antwoordde hij mij 'Amai, wat een miserie. Je bent nog niet afgestudeerd en je begint al met de complicaties'. Dat geldt niet voor jou, want het onderwerp adhesies heeft jou gegrepen in de praktijk, na de nodige jaren ervaring in de chirurgie. Nu ben jij ook bezig met mooie dingen in het adhesie onderzoek. Met jou erbij zal het in ieder geval nooit aan optimisme en vrolijkheid ontbreken om het probleem van adhesies op te lossen.

Drs. Y. Issa, Beste Yama,
Bedankt voor al je inspanningen voor de LAPAD studie en als student- onderzoeker. Je bent nu al een tijdje verder gegaan als onderzoeker van de pancreatitis werkgroep in Amsterdam. Ik ben er van overtuigd dat je daar tot je recht zal komen met je vastberadenheid, oprechtheid en harde werk. Ik wens je alle goeds toe.

De leden van de Dutch Adhesion Group, **Dr. E.J.P. van Santbrink, Dr. R.F.P.M. Kruitwagen, Prof. J. Jeekel, Dr. P.J. Dörr, Dr. R. Leqlerq**. Bedankt voor jullie inbreng en kritische gedachten over manuscripten en onderzoeksplannen. Vanuit een relatief klein land met een relatief kleine groep hebben we het probleem van adhesies weer op de kaart gezet.

Prof. M. Rovers, Beste Maroeska,
Zoals een chirurg het mes hanteert, zo hanteer jij data. Ik heb enorm veel waardering voor je scherpzinningheid.

Dr. F. Keus, Beste Erik,
Onze vruchtbare discussies over de error-matrix-approach bewezen weer eens dat je niet alleen een begaafd clinicus bent, maar ook een bevlogen epidemioloog. Onze samenwerking heeft ons een prachtig artikel opgeleverd. Ik kijk uit naar een vervolg op onze samenwerking.

Alle medeauteurs: Prof. R.P. Bleichrodt, Nienke Kok- Krant, Joyce Wilbers, Barend van den Beukel, Anneke Jilesen.

Alle stafleden van de afdeling Heelkunde, RadboudUMC, Nijmegen. Het was mooi om te zien hoe iedereen betrokken was bij de LAPAD studie.

Alle assistenten en verpleegkundigen van de afdeling Heelkunde, het secretariaat heelkunde, archief medewerkers, de afdeling anesthesie, OK, verkoeverkamer en IC van het RadboudUMC, Nijmegen. De LAPAD studie was een hele logistieke operatie, iedereen bedankt voor het soepel laten verlopen daarvan.

Alle patiënten die hebben deelgenomen aan de LAPAD studie.

De Chirurgen van het Slingeland ziekenhuis Doetinchem. **Susan Lemson,** onze nieuwe opleider en mijn mentor. Onder jouw bezielende leiding, maar vooral ook dankzij de betrokkenheid van alle stafleden, heerst er een fantastische opleidingssfeer, waarbij het nooit

ontbreekt aan ruimte voor een persoonlijke noot. **Felix van Lammeren, Ton van Engelenburg, Koen Reijnders, Sjoerd van der Meer, Erik Staal, Jan Seegers, Dick Scharn, Ruby Krol,** en binnenkort ook **Bas Wiering.** Hartelijk dank voor de warme ontvangst in Doetinchem. Een betere plek om te starten kan een jonge dokter in opleiding tot chirurg zich niet wensen. Ik heb al veel van jullie mogen leren, en dat betreft niet alleen opereren.

De arts-assistenten chirurgie van het Slingeland ziekenhuis. **Theo, Guus, Verena, Pieter, Martelien, Jamilah, Simone, Matthea** en hiervoor ook **Tjaakje, Anne, Niek, Katja** en **Bert.** Het is fantastisch om deel uit te mogen maken van dit team. Het is ongelooflijk mooi om te zien hoe iedereen zich ontwikkelt en waar iedereen mee bezig is. 'De weg naar succes is altijd onder constructie'.

De chirurgen en (oud) arts-assistenten van het ziekenhuis de Gelderse Vallei. Het was een plezier om met jullie te hebben gewerkt. Het is hartverwarmend om te zien hoe jullie betrokken blijven als we elkaar weer eens tegen komen bij onderwijs, chirurgendagen, en last but not least.... vandaag!

Het secretariaat, polikliniek, chirurgische afdelingen, OK, SEH, IC, anesthesie en vele consulenten van het Slingeland ziekenhuis en ziekenhuis de Gelderse Vallei. Een keten is zo sterk als de zwakste schakel, dat geldt ook voor ketenzorg. Bij jullie trek ik na een dag werken de deur met een gerust hart dicht.

Mis amigos de siempre, **Simon, Maurice, Ruben, Dylan, Thomas,** en **Arun.**

Lieve **Barend** en **IJda.** Soms is het echt even afzien in een huishouden met twee promovendi. Dank dat jullie altijd voor ons klaar staan.

Mijn broer **Andrew.** We hebben samen veel meegemaakt. Siblings are born, a brotherhood is forged.

Lieve **Mama,** het is niet altijd gemakkelijk geweest om twee van die mannen alleen op te moeten voeden. We hebben gelachen en gehuild. Toch heeft u me alles geleerd wat een jonge man moet weten. 'Read the Bible, work hard and honestly, and don't complain.' Ik houd van u.

Mijn lieve **Marieke,** al schreef ik het mooiste proefschrift, en stond ik in alle medische journals – had ik de liefde niet, ik zou niet meer zijn dan een dreunende gong of een schelle cimbaal. Ik houd van je.

List of publications

Peer- reviewed medical journals:

Andeweg CS, Berg R, Staal B, **ten Broek RP**, van Goor H. Patient-reported outcomes in diverticulitis: a systematic review and meta-analysis. Submitted

Stommel MW, Strik C, **ten Broek RP**, de Wilt JH, van Goor H. Impact of Adhesiolysis on Clinical and Oncological Results in Colorectal Surgery. Submitted

Stommel MW, Strik C, **ten Broek RP**, van Goor H. Study protocol for a randomized controlled clinical trial to assess the effect and safety of the C-Qur® film adhesion barrier for the prevention of surgical adhesions: CLIPEUS- trial. Submitted

Strik C, Stommel MW, Schipper LJ, **ten Broek RP**, van Goor H. Long-term impact of adhesiolysis during abdominal surgery. Submitted

Strik C, Stommel MW, **ten Broek RP**, van Goor H. Adhesiolysis in patients undergoing a repeat median laparotomy. Submitted

Strik C, **ten Broek RP**, van der Kolk M, van Goor H, Bonenkamp JJ. Health- related Quality of Life and Hospital Costs Following Esophageal Resection. Submitted

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Curriculum vitae

Richard Peter Gerardus ten Broek was born on the 16th of February 1986 in Tilburg, the Netherlands. After graduating from grammar school at the "st. Odulphus lyceum" in Tilburg in 2004, he studied Medicine at the Radboud University in Nijmegen. Early in Medical School he joined the research group of Prof. H. van Goor at the department of surgery, to do experimental, epidemiological and clinical research on adhesion formation and prevention. Further he participated in the implementation of basic life support training for medical students in the new curriculum as one of the first student- instructors.
As a researcher Richard ten Broek has (co-)authored over 20 peer-reviewed articles and book-chapters and has won the award for best presentation at the European Congress on Surgical Infections in 2011.
After graduating from medical school in 2011 he started working as a surgical resident not in training at 'Ziekenhuis de Gelderse Vallei' in Ede. In 2013 Richard ten Broek started his surgical training at the 'Slingeland ziekenhuis' in Doetinchem under the supervision of Dr. F.M. van Lammeren, followed by Dr. M.S. Lemson.


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